American Heart Journal

An international publication for the study of the circulation

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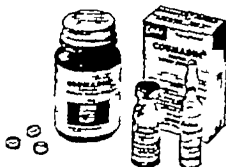
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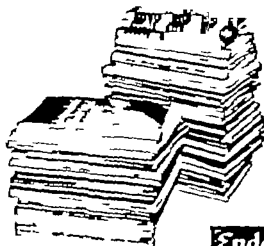
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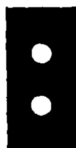
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American Heart Journal

July 1961 Volume 62 Number 1

Editorial

Reflections on the nature of renal tubular reabsorption

Emanuel H. Bresler, M.D.
New Orleans, La.

For many years, particularly at the beginning of this century, renal physiologists were preoccupied with the question of how and how much glomerular fluid is formed. It is now more or less universally agreed that in man over a 24 hour period roughly 180 liters are formed by the process of ultrafiltration. Since in the usual course of events about 1 liter of urine is formed daily, workers in the field of renal physiology are presently concerned with the nature of the forces which contrive to return 179 liters of fluid to the peritubular capillaries each day.

The earliest suggestion in this regard was offered by *Carl Ludwig*,[1] who was the first to appreciate the fact that the volume of urine represented but a small fraction of the total turnover of fluid in the kidney. In his eyes, this organ represented a modified capillary bed with anatomically discrete filtrative and reabsorptive areas separated from one another by the tubular wall. The tubular membrane was thought to have permeability characteristics which differed only slightly from those of the glomerular membrane. This would permit most of the tubular fluid to be drawn freely into the adjacent capillaries in answer to the same oncotic forces which serve to reabsorb filtered fluid in the capillary beds of the body at large. Thus, urine was thought by Ludwig to be formed in a manner very similar to the way in which we conceive of the formation of lymph today.

Since the cells which line most of the tubular wall resemble those in secreting organs, Ludwig's views met with considerable opposition. In closer adherence to Bowman's original suggestions, it was widely believed that most urinary solids were deposited into the tubular lumen by cellular secretion, with small amounts of glomerular fluid, not in excess of the final volume of urine, being formed to wash these down.

Some 40 years ago, Arthur Cushny summarized much of the existing evidence and described the "modern theory of the urinary secretion."[2] In this view, large volumes of fluid are formed by ultrafiltration at the glomerulus, followed by the reabsorption of almost equally large volumes at the tubular level, as originally suggested by Ludwig. However, Cushny's interpretation of the process of tubular reabsorption differed sharply. Since Ludwig's simple concept of an inert tubular membrane could only account for the formation of

From the Research Department, Veterans Administration Hospital, and the Department of Medicine, Tulane University School of Medicine, New Orleans, La.
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urine isosmotic to plasma and could not account for observed differences in composition between urine and plasma. Cushny ascribed reabsorption to a vital activity of tubular cells. The tubular cell was conceived of as a sort of pump which deposited an ideal Locke's solution into the peritubular surround.

In 1948 Wesson, Anslow, and Smith[3] took exception to this nebulous description of the tubular activity and offered in its place a more precise formulation. They agreed with Cushny that most filtered solutes are not free to diffuse across the tubular wall but differed from him by suggesting individual transport systems for each of the impermeant solutes returned to the surrounding capillaries. In the proximal tubule, where the bulk of reabsorption takes place, they postulated a water permeable but sodium impermeable membrane barrier. The force accounting for the movement of large volumes of fluid was described as arising from active transport of sodium with water following passively to achieve osmotic equilibration. They obtained data on the excretion of sodium and water during strong mannitol diuresis which, when interpreted in the light of certain critical assumptions, lent support to their thesis.

That active transport of sodium occurs in some tubular area is implicit in the formation of a urine with a sodium content lower than that of plasma. The micropuncture studies of Richards and associates in the amphibian and of Walker and associates[4] in the mammalian kidney demonstrated that sodium moves against a concentration gradient in some distal regions of the tubule. It is reasonable, therefore, to suppose that a similar active transport mechanism would be required to move sodium across the proximal tubular wall. The fact that micropuncture studies under more or less physiologic conditions have not generally shown a significant sodium concentration gradient between proximal tubular fluid and plasma is readily explained by postulating a high permeability to water of the tubular wall in this area. More recently, micropuncture studies during mannitol diuresis have revealed lower concentrations of sodium in proximal tubular fluid than in plasma.[5] This indicates active transport of sodium in the proximal tubule, at least under conditions of osmotic diuresis. These studies, as well as others, have reinforced the original interpretations of Homer Smith and his collaborators which have served as the framework for much of the thinking in renal physiology during the past decade.

However, certain logical consequences of the construction of tubular activity outlined above lead to difficulties which require close examination. Separate tubular transport systems are required for each molecular and ionic species filtered at the glomerulus and destined to return to the blood stream but not free to diffuse across the tubular wall. When viewed in aggregate, these transport systems constitute an outwardly directed cellular secretory activity of considerable dimensions. In man 179 liters of secreted fluid must be deposited daily in the peritubular area. Though the polarity has been reversed, the role of secretion in the ultimate formation of urine is no less important than that ascribed to it by the Bowman-Heidenhain school of the latter half of the nineteenth century. It has, however, assumed quantitative proportions that probably would have dismayed even the vitalists of that era. However, since the capacity per gram of tissue of the salt secreting glands of certain marine avian species is in this order of magnitude,[7] there are no a priori grounds for supposing that the tubules of the kidney would not be equal to this task.

There are nonetheless greater conceptual difficulties posed by current theory relating to tubular reabsorption. In the ordinary course of events the daily urinary output of salt and water is a very small remainder of two large opposing processes. A small percentile variation in either the amount of sodium filtered without concomitant change in the amount reabsorbed, or vice versa, could lead to large fluctuations in the urinary output well beyond the changes ordinarily observed. It is clear, therefore, that the rate at which sodium is filtered and the rate at which it is reabsorbed remain in remarkably close balance with one another. No satisfactory explanation of how two processes of such dissimilar nature can continue to operate at essentially the same rate has yet been

vanced. The quantity of glomerular fluid formed is related to physical parameters such as hydrostatic and oncotic pressures. Active tubular transport of sodium is regarded to be a chemical process governed by metabolic conditions prevailing in the cell.

One might perhaps imagine that nature has neatly contrived an anatomic balance between the filtering surface and the tubular secretory mass with each of these relatively fixed and capable of only slight variation. This supposition is contradicted by the fact that they may vary widely although almost invariably in close companionship with one another. This is clearly demonstrated in the experiment of Lottspeich and associates,[4] in which the rate of filtration was acutely elevated by the administration of amino acid. Although the filtration rate was nearly doubled, each increment in the filtered load of chloride was accompanied by proportional and almost equal changes in the tubular reabsorption of chloride. Although sodium was not measured in these experiments the same behavior for this ion can be presumed without question. This clearly demonstrates that it is covariance rather than invariance which accounts for glomerulotubular balance.

It is conceivable that this covariance could result from the opening of inactive nephrons. However, such intermittent activity is not thought to occur in the mammalian kidney.[11] We must suppose therefore that the rate of transport of sodium in individual tubules rises and falls with fluctuations in the rate of filtration. How could such a remarkable synchronization occur? Are we to imagine that the renal tubular cell is possessed with the mysterious propensity for sensing the rate of filtration of sodium upstream to it and for promptly and accurately adjusting its pumping rate to match? The conceptual difficulty posed here applies not only to sodium but also to other ions which are largely but not completely reabsorbed. These considerations suggest that current theory in regard to the nature of tubular reabsorption of strong electrolytes may require revision.

What is required is a model of the kidney which might explain, or at least offer reasonable hope of explaining, the close companionship of the volumes of fluid constantly filtered and reabsorbed. A well-known example of such a system has been defined for us in the capillary beds of the body at large, where approximately equal yet large volumes of fluid undergo filtration and reabsorption. This leads us back to Ludwig's concept of the kidney, as described earlier, wherein the turnover of fluid in the kidney arises from the operation of the same forces which operate in capillary beds elsewhere. It will be recalled that Cushny rejected Ludwig's concepts relative to tubular reabsorption because the urine formed would always be isosmotic to plasma and plasma-like in composition. Subsequent studies, which of course were not known to Cushny at the time he was formulating his theory, have revealed that the bulk of reabsorption takes place in the proximal tubule, and that the fluid emerging is isosmotic to plasma and plasma-like in its strong electrolyte composition. Therefore, it now seems reasonable to suppose that the predominant mechanism leading to reabsorption may be one not very different from that originally conceived by Ludwig. This would place at our disposal an alternative model of the renal function wherein both filtration and, to a large extent, tubular reabsorption are governed by a common set of physical parameters. The proximal tubular membrane is here assumed to be essentially freely permeable to electrolytes so that oncotic and hydrostatic forces, similar to those at play in other capillary beds, are free to contribute importantly to the filtration-reabsorption steady state. However, since the permeability characteristics of the glomerular and tubular membranes differ with respect to certain solutes, such as urea, and because some solutes, such as glucose, are actively transported, the conditions leading to a steady state are considerably more complex than those in other capillary beds. All other factors being constant, the degree to which glomerular fluid is

It has been suggested that if the [illegible] flow across the glomerular membrane were [illegible] [illegible]

absorbed will depend on the relative osmotic activity of impermeant solutes within the tubule as compared to that of the impermeant solutes in the peritubular surround.[1] The osmotic activity of the latter will be governed by a number of factors such as the concentration of protein in the plasma of the peritubular capillaries, the rate of deposition of osmotically active solutes, such as glucose, into the peritubular surround, and the rate of plasma washout of these as determined by plasma flow.

The crucial point of difference between what may be termed the physical and secretory approaches to the problem of tubular reabsorption resides in the assumed permeability characteristics of the proximal tubular membrane with respect to strong electrolytes. In the absence of sufficient direct evidence, at least with respect to the mammalian kidney, there has been a natural reluctance to concede that a cellular barrier such as that posed by the tubular wall would permit essentially free diffusion of electrolytes across it.[12] However, in the case of the upper intestinal tract, Ussing[14] has pointed out that the permeability of the mucosal wall with respect to sodium is so great that physical forces predominate over active transport. There would seem to be no a priori reason why a similar predominance of passive diffusion over active transport should *not prevail for the* proximal tubular wall.

In an attempt to gain insight into the problem of whether the proximal tubular wall acts mainly as a pump for sodium or permits free diffusion of this ion, we compared the rate of tubular reabsorption of sodium at high and normal levels of plasma salt.[15] It was reasoned that if the membrane permitted essentially free diffusion, the formation of a hypernatric filtrate would obligate the reabsorption of a hypernatric reabsorbate. Thus paradoxically, more sodium would be reabsorbed by the animal while hypernatremic than at normal levels of plasma salt. On the other hand, if the tubular wall functioned as an active transport system responsive to body needs, the rate of tubular reabsorption should decrease or at least remain unchanged when levels of plasma salt are elevated. The data revealed that although the dogs filtered and excreted more sodium when hypernatremic, as would be expected, they also *reabsorbed* more sodium. Moreover, the increments in sodium reabsorption were proportional to the increments in levels of plasma sodium. This finding that tubular reabsorption of sodium is increased in the face of hypernatremia and total body surfeit of salt favors the operation of an indiscriminate process such as diffusion as the predominant mechanism. When we attempt to interpret these data in the light of the current concept of tubular reabsorption, we are forced to suppose that one or more of the active systems for sodium transport are stimulated to conserve sodium at a time when the dictates of body economy demand excretion.*

There are other observations which are well explained with the modified Ludwigian model of the kidney but require strained interpretation when examined in the light of present-day concepts. For example, it has been postulated[4] that potassium is actively reabsorbed in the proximal tubule only to be secreted by an oppositely directed transport process into the tubule at a more distal locus. Since it has been shown that the concentrations of potassium and sodium remain plasma-like in proximal tubular fluid,[5] it would appear much simpler to suppose that in this area of the tubule they are both reabsorbed as a *result of being passively included in the* filtration-reabsorption stream. If they were each reabsorbed by individual transport systems, these would have to somehow pump at continuously synchronous rates.

An important problem facing renal physiologists is how the kidney operates to maintain a constant extracellular fluid volume. The kidneys of bilaterally adrenalectomized animals maintained in good condition by fixed hormonal replacement regulate volume normally.[1] The transplanted denervated kidney retains the ca-

*In these experiments the elevation of sodium concentration [illegible] the same on both sides of the tubule cell. Therefore we cannot imagine that [illegible] transport process is stimulated by [illegible] gradient. Moreover, in the experiments [illegible] tubular reabsorption of chloride kept pace [illegible] load with no change [illegible] the concentration of [illegible]. The operation of an [illegible] mechanism such as that for glucose [illegible] ruled out by the fact that salt escapes [illegible] at low and high [illegible] load.

pacity to regulate volume normally.[19] It is clear, therefore, that the kidney is capable of regulating the volume of extracellular fluid without regard to a control exerted by the level of any of the adrenal hormones in the circulating blood and without regard to a direct neural control. Aside from the possibility that some unidentified hormone exerts a control over tubular activity, it would appear that renal hemodynamic changes may be responsible for the changes in urinary output observed after contraction or expansion of extracellular volume.

During states of circulatory insufficiency as a result of contraction of plasma volume[9] or heart failure,[11] renal plasma flow falls to very low values. The rate of glomerular filtration may remain normal or is usually reduced to a lesser extent. Under such conditions, presumably because of an increase in intraglomerular pressure, more fluid is filtered from each unit volume of plasma flowing through the glomerulus. The plasma leaving the glomerulus to perfuse the peritubular capillaries would therefore have a higher content of protein. Using the modified Ludwigian model of the kidney, I[*] and others[3,16] have suggested that this increased oncotic activity in the peritubular capillaries could lead to an increased absorption of tubular fluid, thus accounting for the oliguria observed. Other aspects of the altered hemodynamic pattern, such as the reduced rate of plasma washout of osmotically active particles from the peritubular surround, may play equally or perhaps even more important roles in determining the extent of tubular reabsorption. So little is known about possible changes in the distribution of blood flow and pressure relationships in the kidney during circulatory insufficiency that these can only be speculated upon at present.

In summary, the current theory regarding the reabsorption of strong electrolytes postulates the careful metering out, by the tubular cells, of huge but exact proportions of ions in order to form a reabsorbate practically identical to ultrafiltrate in composition. It has been pointed out that if sodium and potassium were largely or exclusively pumped across the proximal tubular wall, it would be necessary to attribute a number of highly unusual characteristics to the transport systems involved. These are: (1) the ability to sense alterations in the rate of filtration and adjust their pumping rates to match; (2) the anomalous characteristic of returning more sodium to the body under certain conditions when the need for excreting salt is great; (3) the ability to synchronize the rates of transport of sodium and potassium so as to maintain a constant and plasma-like ratio of these ions in proximal tubular fluid.

Since the electrolyte composition and volume of reabsorbate is very similar to that of ultrafiltrate, an alternative model of the renal function is proposed in which the large volumes of fluid reabsorbed in the proximal tubules return across an essentially electrolyte-permeable wall in answer to forces similar to, but not identical with, those existing in other capillary beds. The major modifications in the electrolyte composition of urine would be accomplished by active transport systems located in more distal tubular regions. Thus with respect to water and electrolytes, excepting perhaps bicarbonate, the main function of the proximal tubule would be to reduce the volume of ultrafiltrate, whereas the main function of the distal tubular segments would be to alter the electrolyte composition of the fluid finally emerging as urine.

[*] [illegible]

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Clinical communications

Calcium, chelates, and digitalis
A clinical study

Robert S. Eliot, M.D.
*S. Gilbert Blount, Jr., M.D.**
Denver, Colo.

In 1921 Singer[1] aptly described calcium as "the whip and the rein of digitalis." It is recognized that calcium plays a prominent role in provoking and perpetuating cardiac arrhythmias. Calcium, as well as other metallic ions, mimics digitalis in many ways and is synergistic. Therefore, if ionized calcium is decreased, digitalis effect might likewise be diminished.

One of the most effective methods of producing a rapid transient hypocalcemia is through the intravenous use of trisodium ethylenediamine tetraacetate (Na_3EDTA). The term *chelating agent* is derived from the Greek *chelate* meaning claw. A chelate then is a chemical compound formed between a metallic ion and a molecule having two neighboring groups capable of simultaneously combining with a metal to form a ring structure. Na_3EDTA has a powerful and preferential affinity in the binding of calcium. It is the purpose of this paper to report our experience with 92 infusions of Na_3EDTA in 66 patients.

Types of patients and procedure employed

A total of 66 patients received 92 intravenous infusions of Na_3EDTA. Forty-five males and 21 females were studied. Their ages ranged from 9 months to 90 years. Thirty-five patients had unequivocal historical, clinical, and electrocardiographic evidence of a cardiac arrhythmia or conduction disturbance resulting from absolute overdosage of digitalis. Relative digitalis overdosage was not studied except when specifically mentioned. Sixteen patients also had cardiac arrhythmias but had not been on any digitalis preparation for at least 6 weeks. This latter group was composed mainly of patients with arteriosclerotic or rheumatic heart disease. Exceptions will be pointed out later in the text. Three digitalized patients with miscellaneous arrhythmias were also treated. Twelve patients had neither clinical nor electrocardiographic evidence of arrhythmia or cardiac disease. A second infusion was given in 26 patients. Since the results of the second infusion were invariably similar to those of the initial infusion, they will not be discussed separately.

Sixty-six patients received a total of 92 intravenous infusions of Na_3EDTA averaging 3.25 Gm. in 12 minutes (1.25 to 4.0 Gm. in from 5 to 120 minutes). The solution was made up as a 15 mg. per cubic centimeter solution (4 Gm. of Na_3EDTA in 250 c.c. of 5 per cent glucose in water). The Na_3EDTA used was packaged as a 1.0 Gm./5 c.c. aqueous solution.† The

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Table I. First-degree heart block

Patient number, age, sex	Digitalis preparation	ECG before test: P-R (sec.)	EDTA infusion: Dose (Gm.)	EDTA infusion: Time required (min.)	ECG after test: P-R (sec.)	Effect observed: Onset (min.)	Effect observed: Duration
1. H. J., 48, M	None	0.26	3.0	10	0.21	7	60 min.
2. M. H., 82, F	Digoxin	0.29	4.0	12	0.22	10	30 min.
3. A. H., 70, M	Digitalis leaf	0.28	3.5	15	0.21	5	6 hr.
4. L. S., 54, M	Digoxin	0.23	4.0	12	0.20	3	8 hr.
5. A. J., 6?, M	Digitoxin	0.48	3.5	8	0.32	5	30 min.
Average		0.31	3.6	11.4	0.23	6	192 min.

Patients 2, 3, 4, and 5 were taken off digitalis and given oral potassium. Within 10 days all had P-R intervals of less than

average infusion was 255 mg. per minute (range 50 to 800 mg. per minute).

The electrocardiogram was monitored for 3 to 5 minutes prior to each infusion, and records were taken at 1 minute intervals or less during the infusion. The end point was the presence or absence of a change in the rhythm or conduction. Follow-up tracings were recorded after 24 hours in the majority of patients.

Where studied in 32 patients, the serum calcium ranged from 5.2 to 16.2 mEq./L. (average 6.5 mEq./L.) prior to, and from 4.1 to 14.8 mEq./L. (average 5.3 mEq./L.) after the infusion. Serum potassium ranged from 2.8 to 5.2 mEq./L. (average 3.8 mEq./L.) and did not change. Sodium, carbon dioxide, blood urea nitrogen, and chloride were also unaffected. All samples of blood were drawn from the arm opposite the site of infusion. Studies on serum electrolytes were discontinued later because of the uniform finding of a hypocalcemic effect and the doubtful relationship of this value to actual ionized calcium. Levels of serum phosphorus were not run. Blood pressure, pulse, respiratory rate, clinical signs of hypocalcemia, and subjective complaints of digitalis intoxication were observed before, during, and after all infusions.

Results

First-degree atrioventricular block. All 5 patients studied had an average shortening of 0.08 second of the P-R interval, and the depression of the S-T segment was lessened (Table I). The heart rate decreased 25 per cent in 4 patients, and was 10 per cent increased in Patient 1.

COMMENT. All patients were digitalized and had evidence of absolute overdosage except Patient 1, who had proved primary hyperparathyroidism. It is of interest that the response in this patient was similar to that in those who were overdigitalized. First-degree atrioventricular block disappeared permanently in the overdigitalized patients when digitalis was withdrawn and administration of oral potassium chloride was instituted. We assume, therefore, that the prolonged P-R interval was due to digitalis overdosage.

Serum calcium (mEq./L.)		Serum potassium (mEq./L.)		Subjective symptoms		Remark
Before	After	Before	After	Before	After	
16 2	14 8	3 8	3 6	0	0	Primary hyperparathyroidism
5 2	4 8	4 0	4 1	0	0	
6 4	5 0	3 6	3 8	++	0	Nausea remitted permanently Arm pain above infusion site
5 8	4 4	3 1	3 3	+++	0	Nausea remitted permanently Arm pain above infusion site
—	—	—	—	0	0	Arm pain above infusion site
8 4	7 4	3 6	3 7			

0 20 second and no subjective complaints. Before: Before infusion After: Immediately after 1 hr l

Second-degree atrioventricular block Five patients with absolute digitalis overdosage had second-degree atrioventricular block Four of the 5 patients reverted to sinus rhythm with first degree block and one of these (Patient 6) developed a normal P R interval (Table II) With the exception of elimination of premature ventricular contractions the ECG of the other patient was unchanged (Patient 9) although his rhythm later reverted to normal sinus rhythm when oral potassium was administered and digitalis withdrawn The electrocardiograms of all patients in this group maintained the Na_2EDTA effect when digitalis was removed and oral potassium chloride was given

Patient M W deserves special mention This 9 month old Negro boy who weighed 8 5 kilograms had many congenital anomalies including involvement of the renal and cardiovascular system He had developed congestive failure and had been on maintenance digoxin for several weeks The child through error had received 0 6 mg of digoxin (10 times his maintenance dose) Two hours and 20 minutes later profuse vomiting and diarrhea developed the blood pressure fell and the child's condition appeared to be terminal The ECG revealed second degree A V block Infusion of Na_2EDTA was administered and 10 minutes thereafter his blood pressure returned to normal vomiting ceased and he took and retained oral fluids Twenty minutes later and after he had received 1 0 Gm of Na_2EDTA the ECG reverted to sinus rhythm with a first-degree A V block (Fig 2) The rhythm returned to second degree A V block on several occasions but could be restored to first-degree block merely by speeding up the rate of infusion However tetany developed 30 minutes after the start of the infusion and after 1 2 Gm of Na_2EDTA had been given At this time the ECG showed sinus arrest with a slow nodal rhythm Two cubic centimeters of 10 per cent calcium gluconate were given intravenously and irreversible ventricular fibrillation shock and death ensued almost immediately I[illegible] potassium chloride was ineffectual

Table II Second degree A V block in patients with dig[redacted] intoxication

Patient number, age, sex	Digitalis preparation	ECG before test	EDTA infusion: Dose (Gm)	EDTA infusion: Time required (min)	ECG after test	Effect observed: Onset (min)	Effect observed: Duration	Serum calcium (mEq/L): B	Serum calcium (mEq/L): A	Serum potassium (mEq/L): B	Serum potassium (mEq/L): A	Subjective symptoms: B	Subjective symptoms: A	Remarks
6 M W 74 F	Digitoxin	Type II A V block	1 0	19	Sinus rhythm P R 0 20 sec	8	Permanent	6 4	5 1	5 1	5	++++	0	N ea d mon unturb unct rem tted during infu ion
7 J M 72 M	Digitalis leaf	P A T with 2 1 A V block	2 5	10	First-degree block P R 0 33 sec	10	35 min	—	—	—	—	—	—	Arm pa ibow infusion site
8 L K 60 M	C talin	Type I second degree A V block Wenckebach phenomenon	4 0	9	First degree block P R 0 ?? sec	10	Permanent	6	4 9	3 4	3 6	—	—	—
9 K T 71 M	Digitoxin	Type I second degree A V block Wenckebach and 12 PVCs/min	4 0		Second degree A V block No PVC	6	Permanent	5 9	4 7	3 7	3 9	+++	0	Nausea remitted during infusion
10 M W 9 mo M	Digoxin	Second-degree A V block	1 2	10	Sinus rhythm First degree A V block P R 0 21 sec	10	Permanent	—	—	—	—	+++	0	Developed tetany and died in ventricular tachycardia when I V calcium was given Child had many severe congenital anomalies Vomiting ceased
Average			2 9	11		8 8	Permanent	6 2	4 9	4 1	4 2			

All of the electrocardiograms returned to normal within 14 days after admission to hospital ... of oral potassium chloride and ... withdrawal of digitalis
B Before infusion A Immediately after ... P A T Paroxysmal atrial tachycardia PVC Premature ventricular contraction

Table III Complete A V block in patients believed to be digitalis intoxicated

Patient number age sex	Digitalis preparation	ECG before test	EDTA infusion: Dose (Gm)	EDTA infusion: Time required (min)	ECG after test	Effect observed: Onset (min)	Effect observed: Duration	Serum calcium (mEq/L): B	Serum calcium (mEq/L): A	Serum potassium (mEq/L): B	Serum potassium (mEq/L): A	Subjective symptoms: B	Subjective symptoms: A	Remarks
11 A H 70 M	Digitoxin	Complete A V block R tes trial 89 entricular 40	3 0	15	First degree A V block P R 0 23 sec	10	Perma nent	6	4 9	3 6	3 6	++	—	Nausea vomited Arm pain above infusion site
12 L R 7 F	Leaf	Complete A V block Atrial fibrillation with entricular rate of 36	3 5	70	No change	10	30 min	6 5	5 1	3 1	3 3	—	—	Died
13 R P 64 M	Leaf	Complete A V block P tes trial 65 entricular 38	3 0	9	Sinus rhythm P R 0 20 sec	5	Perma nent	—	—	—	—	++	—	Nausea vomited Arm pain above infusion sit
4 R W 74 M	Digoxin	Complete A V block R tes trial 68 entricular 40	4 0	22	First-degree A V block P R 0 24 sec	10	Perma nent	—	—	—	—	—	—	—
15 A B 60 M	Digitoxin	Complete A V block R te trial 30 entricular 40	3 5	30	Rat 68 per min t P R 0 16 sec	11	60 min	—	—	—	—	—	—	—
16 B H 74 F	Digoxin	Rates trial 72 entricular 36	4 0	10	First degree A V block P R 0 33 sec	5	20 m	5 6	4 4	3 9	4 1			Arm pain above infusion site
1 M I 60 M	Digitoxin	Rates trial 85 entricular 35	2 0	20	Complete block trial 95 tricular 12	—	—	—	—	—	—	—	—	Low dosage with slo administration Reverted to sinus rhythm on KCl and removal of digitalis
Average			3 8	18		8 5	—	6 1	4 8	3 5	3 7			

Before infusion A Immediately after [illegible]

Table IV. A-V dissociation believed to have resulted from digitalis intoxication

Patient number age sex	Digitalis preparation	ECG before test	EDTA infusion: Dose (Gm.)	EDTA infusion: Time required (min.)	ECG after test
22 B.H. 60 F	Digitoxin	A-V dissociation	3.0	30	Sinus rhythm
23 E.S. 48 F	Digoxin	A-V dissociation	2.0	15	First degree A-V block P-R 0.24 sec.
24 B.T. 80 F	Digitoxin	A-V dissociation	3.0	10	Sinus rhythm
25 G.S. 65 F	Digoxin	A-V dissociation	3.5	10	Sinus rhythm
26 R.N. 61 M	Digoxin	A-V dissociation	4.0	12	Sinus rhythm
Average			3.1	13.4	

Table V. Summary of 12 patients with atrial fibrillation, 7 of whom were digitalized

Patient number	Digitalis preparation	ECG before test	EDTA infusion: Dose (Gm.)	EDTA infusion: Time required (min.)	ECG after test
24–33	3 Digitoxin 3 Digoxin 1 Digitalis	Atrial fibrillation	3–4	10–20	Atrial fibrillation, 26 per cent increase in ventricular rate. Range 15–35 per cent
34–38	None	Atrial fibrillation	3–4	10–20	Atrial fibrillation, 12 per cent increase in ventricular rate. Range 10–15 per cent

COMMENT. This patient's course suggests the following: (1) Na_2EDTA was able to reverse the cardiac arrhythmia secondary to considerable absolute digitalis overdosage. (2) There was a narrow margin between tetany and therapeutic effect in this child. (3) There is profound danger in the use of intravenous calcium in digitalized patients even when Na_2EDTA is present. Death rarely results from tetany and thus intravenous calcium should probably be withheld if at all possible. The danger of ventricular fibrillation is greater than that of tetany. (4) The dramatic cessation of gastrointestinal symptoms pursuant to Na_2EDTA was striking and is perhaps an

Effect observed		Serum calcium (mEq./L.)		Serum potassium (mEq./L.)		Subjective symptoms		Remarks
Onset (min.)	Duration	Before infusion	After infusion	Before infusion	After infusion	Before infusion	After fusion	
25	24 hr	6 4	4 8	3 4	3 3	—	—	Arm pain abov infusion sit
7	Permanent	—	—	—	—	—	—	——
8	Permanent	5 4	4 1	3 5	3 5	—	—	Arm pain above infusion sit
6	12 hr	7 1	5 8	3 6	3 7	++	—	Arm pain bove infusion site Nausea remitted
8	12 hr	7 0	5 6	3 7	3 9	++	—	Nausea rem tted
7 7	—	6 4	5 1	3 6	3 6			

Effect observed		Serum calcium (mEq./L.)		Serum potassium (mEq./L.)		Subjective symptoms		Remarks
Onset (min.)	Duration (hr.)	Before infusion	After infusion	Before infusion	After infusion	Before infusion	After infusion	
10	1 3	6 8	5 4	4 0	3 9	1/7	0/7	2 of the 7 patients had arm pain bove the fusion site
10	1	6 2	5 1	3 9	3 9	0	0	3 of the 7 patients had arm pain abov the fusion site

indication that the subjective complaints of digitalis intoxication are also relieved by the binding of ionized calcium

Complete atrioventricular block. Ten patients with complete heart block were studied and in 7 of these the block was believed to be the result of absolute digitalis overdosage Sinus rhythm or first-degree block replaced the complete block in 5 of these 7 patients on digitalis (Fig 3) Failure in one patient (Patient 17) was later converted when oral potassium was administered and digitalis was withdrawn (Table III) It should be noted that the amount of Na_3EDTA was small and slowl infused in this patient Another patie

Table VI Summary of findings in patients with premature ventricular contractions on digitalis

Patient number age sex	Digitalis preparation	ECG before test	EDTA infusion: Dose (Gm.)	EDTA infusion: Time required (min.)	EDTA infusion: ECG after test
39 O D 63 F	Digoxin	Bigeminy with re-entry	3 0	12	First degree A V block P R 0 27 sec.
40 E L 58 F	Digitoxin	Bigeminy with re-entry	2 5	20	N S R
41 R T 65 M	Digoxin	Trigeminy	3 5	7	N S R
42 L K 70 M	Digitalis	Trigeminy	4 0	10	N S R
43 H B 69 M	Digoxin	17 PVC/min re-entry	3 5	10	N S R
44 M M 62 M	Digoxin	12 PVC/min	4 0	15	2 PVC/min
45 J T 70 F	Digitoxin	17 PVC/min	4 0	10	17 PVC/min
46 R J 8 M	Digoxin	15 PVC/mi	3 5	20	14 PVC/min
47 T H 70 F	—	Bigeminy with re-entry	4 0	10	No change
48 H V 60 M	—	Bigeminy with re-entry	4 0	10	No change
49 V P 45 M	—	18 PVC/min	4 0	12	15 PVC/min
50 G S 71 M	—	11 PVC/min	4 0	12	6 PVC/min
51 W S 64 M	—	7 PVC/min	3	10	7 PVC/m
52 W L 64 M	—	12 PVC/min	4 0	10	11 PVC/min
Average			3 7	11	

failure (Patient 12) had had a history of Stokes-Adams attacks for 5 years. She was refractory to Isuprel ephedrine molar lactate and many other drugs. Autopsy revealed extensive coronary atherosclerosis and myocardial fibrosis which had almost obliterated the atrioventricular node.

The other 3 patients who were not on digitalis had electrocardiographically documented complete heart block of 2 to 5

Effect observed		Serum calcium (mEq/L)		Serum potassium (mEq/L)		Subjective symptoms		Remark
Onset (min.)	Duration	Before infusion	After infusion	Before infusion	After infusion	Before infusion	After infusion	
12	Permanent	—	—	—	—	0	9	Circumoral paresthesia Arm pain
5	3 hr	5.6	4.5	4.0	3.8	++	—	Nausea remitted
5	Permanent	—	—	—	—	++	—	Nausea remitted
7	2 hr	6.2	5.1	3.8	3.8	—	—	Arm pain
5	1 hr	—	—	—	—	—	—	Arm pain
10	50 min	5.8	5.0	4.2	4.2	++	—	Arm pain
8	1 hr	—	—	—	—	++	—	Epicardial metastasis of carcinoma of breast
8	90 min	6.4	5.9	3.6	3.6	—	—	Acute thrombosis of right pulmonary artery
—	—	5.9	5.0	3.9	3.9	—	—	Circumoral paresthesia
—	—	—	—	—	—	—	—	Extensive coronary atherosclerosis Arm pain
—	—	6.1	5.9	4.1	4.0	—	—	Chronic myocarditis and myocardial fibrosis
—	—	5.8	4.9	4.3	4.4	—	—	—
—	—	—	—	—	—	—	—	—
—	—	5.9	4	4.0	3.9	—	—	Circumoral paresthesia Arm pain
7.5		5.8	5.1	4.0	4.0			

years duration which was believed to be due to coronary atherosclerosis. These patients were refractory to trials of Isuprel, ephedrine, and lactate. Their response to Na_2EDTA was also uniformly negative.

COMMENT. Thus, with one possible exception (Patient 17), when digitalis was considered to be the cause of the block, infusion of Na_2EDTA was effective. In 3 patients who were suspected of having

Table VI. Summary of findings in patients with premature ventricular contractions on digitalis

Patient number, age, sex	Digitalis preparation	ECG before test	EDTA infusion: Dose (Gm.)	EDTA infusion: Time required (min.)	ECG after test
39 O D, 63 F	Digoxin	Bigeminy with re-entry	3.0	12	First degree A V block, P R 0.2 sec
40 E L, 58 F	Digitoxin	Bigeminy with re-entry	2.5	20	N S R
41 R T, 65 M	Digoxin	Trigeminy	3.5	7	N S R
42 L K, 0 M	Digitalis	Trigeminy	4.0	10	N S R
43 H B, 68 M	Digoxin	17 PVC/min re-entry	3.5	10	N S R
44 M M, 62 M	Digoxin	12 PVC/min	4.0	15	2 PVC/min
45 J T, 70 F	Digitoxin	17 PVC/min	4.0	10	17 PVC/min
46 R J, 58 M	Digoxin	15 PVC/min	3.5	20	14 PVC/min
47 T H, 70 F	—	Bigeminy with re-entry	4.0	10	No change
48 H V, 60 M	—	Bigeminy with re-entry	4.0	10	No change
49 V P, 45 M	—	18 PVC/min	4.0	12	15 PVC/min
50 G S, 71 M	—	11 PVC/min	4.0	12	6 PVC/min
51 W S, 64 M	—	7 PVC/min	3.5	10	7 PVC/min
52 W L, 64 M	—	12 PVC/min	4.0	10	11 PVC/min
Average			3.7	11	

failure (Patient 12) had had a history of Stokes Adams attacks for 5 years. She was refractory to Isuprel, ephedrine, molar lactate, and many other drugs. Autopsy revealed extensive coronary atherosclerosis and myocardial fibrosis which had almost obliterated the atrioventricular node.

The other 3 patients who were not on digitalis had electrocardiographically documented complete heart block of 2 to 5

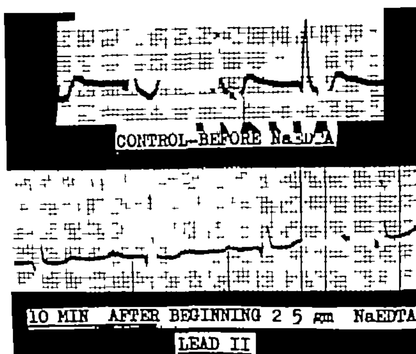


Fig 1 A J (Patient 5) Marked first-degree A V block with an initial P R interval of 0 48 sec and depressed S-T segments in the control tracing After 2 5 Gm of Na_2EDTA the P R interval becomes 0 32 sec and the S-T segment approaches normal The heart rate has gone from control of 84/min to 64/min

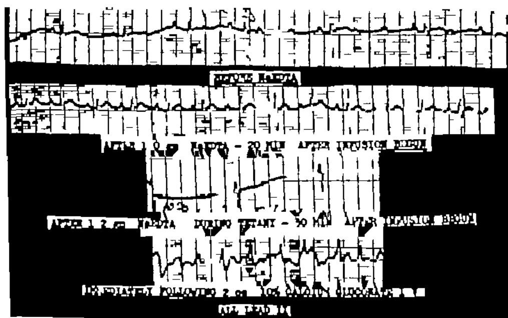


Fig M W (Patient 10) 9 month old Negro boy with renal and cardiovascular anomalies who had received by error 10 times his calculated maintenance dose of digoxin In the upper tracing the patient developed varying A V block After 1 0 Gm of Na_2EDTA sinus rhythm returned After 1 2 Gm of Na_2EDTA tetany developed and sinus arrest with slow idionodal rhythm ensued Immediately after 2 of 10 per cent calcium gluconate intravenously reversible chaotic ventricular rhythm and death occurred

Two digitalized patients with premature atrial contractions failed to respond and at autopsy one had a large right atrial mural thrombus.

Effect of Na_3EDTA on the subjective complaints of digitalis intoxicated patients. Fourteen of the 36 patients with digitalis intoxication had visual color disturbances, anorexia, nausea, vomiting, diaphoresis or apathy in varying combinations. All of the patients experienced relief of symptoms during infusion of Na_3EDTA; such relief usually occurred before a change in the arrhythmia.

Pain in the arm above the site of infusion occurred in 26 (40 per cent) of 66 patients and was ameliorated by warm packs or massage of the site of the pain, and occasionally by slowing or diluting the infusion.

No significant consistent change in blood pressure occurred. All changes were within the limits of error of the cuff technique, the exceptions were in 3 apprehensive patients who had a 25 per cent elevation in systolic blood pressure.

Discussion

Although calcium was recommended in the treatment of heart ailments over a century ago (Blake, 1841), it was Ringer, Howell, and Boehm[9] who delineated our understanding of the effects of calcium and other electrolytes on cardiac action.

The present clinical use of calcium was dramatically introduced in 1928 when an Englishman by the name of Lloyd[9] attached himself to an electrocardiograph and gave himself an intravenous injection of 8 c.c. of 10 per cent calcium chloride. Within a minute of the time of injection he developed a sensation of warmth which progressed to dizziness, pupillodilatation, upward deviation of the eyes, extensor spasm, rigor of the masseters, and respiratory failure. Simultaneous with these events the electrocardiogram demonstrated frequent extrasystoles, ventricular fibrillation, and then no oscillations at all. His colleagues pounded on his chest and injected intracardiac epinephrine. After 5 minutes of asystole the heart began to beat again. After this experience Dr. Lloyd edited a lucid paper on the dangers of intravenous calcium, and it might be added that his name has since been notably absent from the literature on this subject. Recent investigations have substantiated his findings.

From the time of Lloyd there has been an extensive investigation into the role of calcium in cardiac action, although much remains to be learned at the myocardial cellular level.

Currently, it is believed that the effect of digitalis and calcium is at the level of the cell membrane where it produces a change in permeability which causes a migration of potassium from the cell.[10] Animal experiments demonstrate a negative potassium balance in the coronary circulation during digitalization.[11] This negative balance can be exaggerated by digitalis overdosage.

It is the feeling of Blackmon that available circulating potassium in the case of digitalis intoxication is adequate, but that it cannot enter the cell because of alterations in the cell membrane. Na_3EDTA can reverse digitalis induced arrhythmias. It is postulated that this is accomplished by binding the calcium ion and thus depotentiating digitalis, which then permits the return of endogenous potassium into the potassium-depleted myocardial cell.

We believe that one of the most important factors in the success of this form of testing is the size of the Na_3EDTA dose and the rapidity with which it is given. In our experience a test should not be considered to be negative unless the patient has received at least 3.0 Gm. of Na_3EDTA in less than 12 minutes, or unless clinical evidence of hypocalcemia develops. If Chvostek's sign develops it is probably of more significance in determining the degree of binding of the ionized calcium than are levels of serum calcium ascertained in the laboratory. We believe that low dosage and slow administration are the reasons for the failure to reverse the conduction disturbances in Patient 18 and may well account for some treatment failures by other investigators[12, 14] who have used smaller doses over longer periods.

The evaluation of results with premature ventricular contractions, because of the variability, is more difficult than with other more stable rhythms. In our experience, these conduction aberrations are much more elusive and inconsistently related to Na_3EDTA therapy.

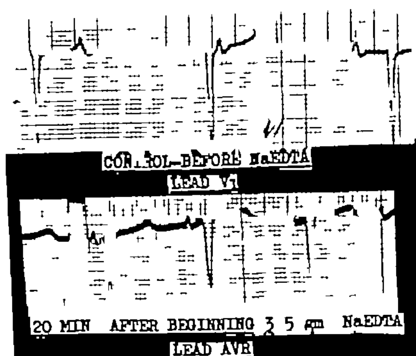


Fig 3 A B (Patient 15) a 60-year-old Negro who had received a additional 0 5 mg of digoxi over his maintenance dosage The patient developed complete heart block 6 hours later After 20 minut inf ion of 3 5 Gm of Na EDTA the patient developed sinus rhythm

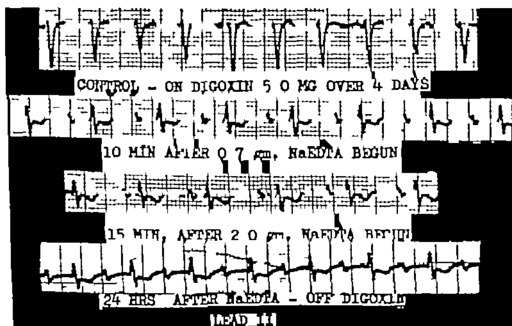


Fig 4 E S (Patient 23) 48 year-old white woman who received 5 0 mg of digoxi over a period of 4 day while in renal shutdown The patient developed A V di sociation which reverted t first-degree A V block (P R of 0 24 sec) w thin 15 minutes of begin ing infusion of 2 0 of Na EDTA Twenty four hours thereafter first-degree A V block was more pronounced bu di sociat on did not return (only uppermost tracing is Lead V)

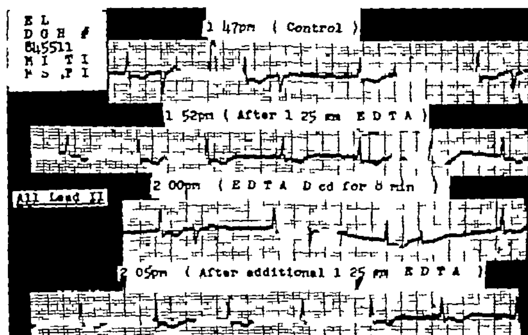


Fig. 5. E. L. (Patient 40). 38-year-old white woman with rheumatic heart disease, atrial fibrillation and congestive heart failure who had taken 0.3 mg. of digitoxin over her usual maintenance dosage. Within 24 hours she developed bigeminy; this disappeared 5 minutes after 1.25 Gm. of Na_3EDTA was given and the infusion was stopped immediately. The bigeminy returned within 8 minutes and the effect was repeated with addition of 1.25 Gm. of Na_3EDTA.

Out of the 66 patients treated, there were only 3 patients who had no evidence of absolute digitalis overdosage and did respond to Na_3EDTA. Lack of response to Na_3EDTA in 2 of the 3 who did have evidence of absolute digitalis overdosage could well be explained on the basis of slow infusion and inadequate dosage. Six patients who failed to respond were found at autopsy to have evidence of cardiac pathology which alone could have accounted for the arrhythmia.

Subjective symptoms of digitalis intoxication, when present, responded in all patients. In every patient in whom the arrhythmia or conduction disturbance permanently or temporarily responded to intravenous Na_3EDTA, the withdrawal of digitalis and addition of oral potassium chloride maintained the response. Thus the drug was an excellent means of predicting the effectiveness of withdrawal therapy which usually requires days to evaluate.

In our experience the drug has been relatively ineffective in the treatment of arrhythmias due to causes other than digitalis, but it is still too early to be certain as to its value in differentiating between organic arrhythmias and those induced by digitalis or calcium potentiating situations. Its effect is so transient in many instances that it is often not a practical therapeutic tool, but does appear to have great value in predicting the efficacy of administration of oral potassium and withdrawal of digitalis.

Na_3EDTA has been implicated as a renal toxic agent in much higher doses given over longer periods.[11] Hemorrhagic diathesis are also reported,[12] but the major clinical danger is tetany. This is a rare occurrence, seen only once in 92 separate infusions. However, if tetany occurs, it would appear advisable to withhold intravenous calcium if at all possible, since the myocardium appears to be acutely sensitive to calcium under these circumstances.

Summary and conclusions

1. Sixty-six patients who ranged in age from 9 months to 90 years received 92 infusions of trisodium ethylenediamine tetraacetate (Na_3EDTA) in the treatment of

cardiac arrhythmias or conduction disturbances Twelve of these patients however had no evidence of cardiac disease arrhythmia or conduction disturbances Thirty six patients were digitalis intoxicated Eighteen had arrhythmias and were not receiving digitalis

2 Na_2EDTA was effective in treating arrhythmias in most digitalis intoxicated patients but the drug was more unreliable in the treatment of arrhythmias in undigitalized patients

3 When Na_2EDTA was effective permanently or transiently in reversing the arrhythmia withdrawal of digitalis plus administration of oral potassium chloride perpetuated or reinstituted normal sinus rhythm

4 Our findings indicate that in adults a minimum of 3 0 Gm of Na_2EDTA should be given within 12 minutes if possible before a result is considered to be negative It is postulated that low dosage over prolonged periods may account for the variability in results by other authors

5 Tetany occurred in one severely intoxicated 9 month old child who died of irreversible ventricular fibrillation when intravenous calcium was given We caution against the dangers of intravenous calcium in this particular circumstance

6 The subjective complaints of digitalis intoxicated patients were relieved during the infusion in all 14 patients in whom the problem existed This effect usually preceded and predicted the normalization of the ECG relative to the digitalis-induced effect

7 Six patients whose arrhythmias or disturbances in conduction were refractory to Na_2EDTA died and were autopsied and both gross and microscopic pathology of the conduction system was found which could have accounted for the arrhythmia produced

8 Arm pain circumoral paresthesias and apprehension occurred in 40 per cent of the patients The arm pain was readily relieved by massage and warm packs The other symptoms could be relieved by slowing the rate of the infusion

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The vectorcardiogram before and after myocardial infarction Superimposition of serial loops

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Vectorcardiographic diagnosis of myocardial infarction depends upon the demonstration that the electrical forces of ventricular depolarization differ in a particular way either from a normal or an abnormal pattern (e.g., left ventricular hypertrophy) or from a pattern known to have existed previously in the same patient. Authority for the former derives in part from electrocardiographic and vectorcardiographic patterns established by painstaking correlation with autopsy material. Changes which occur in association with clinical episodes of acute myocardial infarction lend additional validity to the belief that certain patterns do in fact represent infarction of the myocardium. This report deals with 19 cases in which vectorcardiograms were obtained before and after myocardial infarction.

Material and methods

The vectorcardiogram lends itself to a study of changes by superimposition of serial tracings. Vectorcardiograms taken on 10 patients (Group I) before and after the occurrence of a first myocardial infarction were studied in this manner (Cases 1-10, Tables I and III). The vectorcardiographic loops were transferred to white cards by their projection through a photographic enlarger. Accurate superimposed reproductions were obtained in this way (Figs. 1-6). This provided a practical method of detecting changes which appeared in association with a first clinical myocardial infarction. One of the control vectorcardiograms was normal, one was abnormal but not diagnostic, and 8 displayed left ventricular hypertrophy, intraventricular block, right bundle branch block, and right ventricular hypertrophy (Table I).

Similar studies were carried out in 9 additional patients (Group II) with a past history of myocardial infarction when first seen. These patients subsequently suffered a second myocardial infarction (Cases 11-19, Tables II and IV). In this group the first vectorcardiogram displayed signs of the old infarct and the second one changes associated with the observed clinical episode of recurrent infarction. All tracings in this group displayed signs of left ventricular hypertrophy (Table II).

In each case three pairs (horizontal, sagittal, and frontal) of superimposed be

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fore and after loops as well as electrocardiograms and orthogonal leads X Y and Z were obtained

Autopsy was performed in 4 of the 19 patients and in all of these the vectorcardiographic diagnosis was confirmed

All vectorcardiograms were recorded by means of the double cube reference system with positive polarity The instruments and recording techniques have been described elsewhere

Results

The results are summarized in Tables I IV Changes associated with clinical infarction occurred in at least two of the three orthogonal leads X Y and Z in each of the 19 cases (Tables I and II) The Z axis was modified in 16 cases the Y axis in 17 and the X axis in 16 Changes were seen in the initial and/or early part of the loops in all cases The end or terminal appendage tended to be more stable In Case 14 the only change was reversal in the direction of inscription of the initial forces in the horizontal projection (Y axis) The direction of inscription of the initial forces changed from counterclockwise to clockwise in the horizontal plane in 10 cases and in the frontal plane in 12 cases A change in direction of inscription of the body in the horizontal QRS loop occurred in 5 cases and in the frontal projection in 9 cases

Inferior orientation of the initial forces was present prior to infarction in all 10 of the cases of Group I and reversal to superior orientation occurred in 9 of them 16 to 33 time markings from the 0 point† Initial forces with superior orientation appeared for the first time in 6 of the 10 cases (Cases 1 4 5 7 8 and 9 Table I) in association with the first clinical episode of myocardial infarction In 3 additional cases the initial vectors continued to point downward after clinical infarction occurred but reversed to superior orientation much earlier in the QRS interval i e 7 9 and 5 time markings from the 0 point as compared to 22 16 and 24 markings respectively in the preinfarction vectorcardiograms (Cases 2 3 6 Tables I and III and Fig 1) Vectorcardiographic signs of inferior myocardial infarction were present in all 9 cases

Only in Case 10 of those with a first infarct was an isolated anterior wall lesion present and the sole vectorcardiographic change was increased posterior displacement of the body early in the QRS interval (Fig 2)[4] Diagnostic signs of anterior infarct were observed in 5 additional cases of Group I (Cases 1 2 3 6 and 7) increased posterior displacement early in the loop in Case 1 (Fig 3) change to an entirely

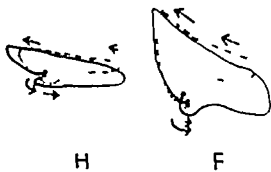


Fig 1 Case 3 The first vectorcardiogram shows left ventricular hypertrophy the second one shows anterior inferior septal and lateral myocardial infarction

Key I Figs 1-4 the solid line = horizontal (*H*) and frontal (*F*) projections prior to infarction and the broken line = the vectorcardiographic projections after first infarct II Figs 5 and 6 the solid line vectorcardiograms were recorded after first infarct and the broken line vectorcardiograms after second infarct Solid arrows indicate direction of inscription of solid line vectorcardiograms and the broken arrows the broken line vectorcardiograms

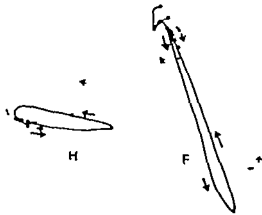


Fig 2 Case 10 The first vectorcardiogram shows left ventricular hypertrophy the second the signs of anterior myocardial (Key to Fig 1)

X = Right left Y = P Z = posterior
†Each time marking ed 0 0025 sec nd

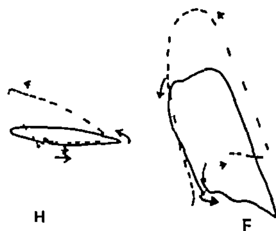


Fig 3 Case 1 Changes diagnostic of anterior and inferior myocardial infarction appear in association with first myocardial infarction The changes are confined to the early portion of the QRS loop (See Key to Fig 1)

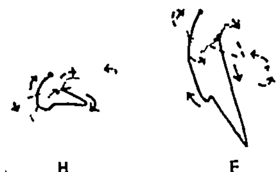


Fig 4 Case 7 The first vectorcardiogram is characteristic of right ventricular hypertrophy the second one shows anterior inferior and septal myocardial infarction Right bundle branch block has appeared in the second vectorcardiogram The QRS interval of the first vectorcardiogram is 0 085 second that of the second one is 0 115 second (See Key to Fig 1)

posterior position of the body of the QRS loop in Cases 2 6 and 7 (Fig 4) and concavity of the centrifugal limb in Case 3 (Fig 1) The alterations were especially striking in Case 7 in which the preinfarction vectorcardiogram showed signs of right ventricular hypertrophy (Fig 4)

Increased magnitude of various measurements and reorientation of initial and/or early forces also occurred in association with a second clinical infarct (Group II) In Cases 11 13 17 18 and 19 first observed after an anterior infarction had occurred the QRS forces were inferior for the first 19 14 16 and 24 time markings in Cases 11 13 17 and 18 respectively in Case 19 the entire QRS loop was inferior In all 5 cases a second clinical episode of myocardial infarction occurred this time in the posterior wall and the initial forces were observed to change from inferior to superior orientation in each instance (Figs 5 and 6 Table IV)

Thus in the combined series of 18 cases of inferior infarction orientation of the earliest forces changed from inferior to superior in 11 in association with clinical infarction Almost all measurements of the initial or early superiorly oriented forces were abnormal in the 18 cases with inferior infarct in Groups I and II (Cases 1 9 11 19) the sweep was greater than the upper limit of normal (mean +2 standard deviations) in 16 the superior inferior ratio in 17 the duration of the initial or early superior forces in 17 and the maximal

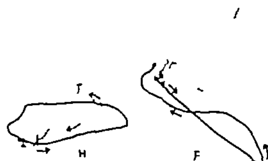


Fig 5 Case 19 The first vectorcardiogram displays anterior infarction the second one shows anterior inferior septal and lateral myocardial infarction The QRS interval in the second vectorcardiogram has increased from 0 092 to 0 187 second because of the development of nonspecific intraventricular block (See Key to Fig 1)

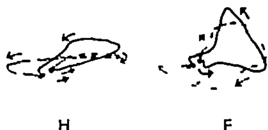


Fig 6 Case 13 The solid line vectorcardiogram displays anterior and septal myocardial infarction the broken line vectorcardiogram displays inferior and lateral in addition to the anterior and septal infarcts The terminal part of the QRS loop has changed significantly The QRS interval of the first vectorcardiogram is 0 085 second that of the second one is 0 102 second (See Key to Fig 1)

superior vector in 7 cases.[1] In association with a second infarct the earliest forces increased or decreased in magnitude, presumably depending on the location of the old and new lesions in respect to each other; the occurrence of anterior infarction in a patient with a previous posterior wall lesion caused a decrease in the magnitude of the diagnostic measurements associated with the old infarct (Case 16, Table IV).

The earliest forces in the frontal plane were counterclockwise in 8 of the 9 cases (Cases 1-6, 8, 9) prior to the occurrence of primary inferior infarction, but changed to

Table I. Vectorcardiographic data in Cases 1-10

Case number	Changes in X Y Z axes	Orientation of earliest forces 1st	Orientation of earliest forces 2nd	Direction of inscription: Earliest forces (1st, 2nd)	Direction of inscription: Body (1st, 2nd)	VCG Dx 1st	VCG Dx 2nd
1	Y− Z−	LAD	LAU	cc (H) cc cc (F) c	cc (H) cc cc (F) cc	LVH	LVH Ant Inf
2	Y− Z−+	RAD	RPDU	cc (H) cc (F)	cc (H) cc cc (F) cc	LVH IV block	LVH IV block Lat Inf Sept
3	Y− Z−	RAD	LADU	cc (H) cc cc (F) c	cc (H) cc cc (F) cc	LVH	LVH Ant Inf Sept
4	X− Z−	LAD	RAU	cc (H) c cc (F) c	cc (H) cc cc (F)	Normal	Inf Sept
5	X−+ Y−+ Z−	RAD	RAU	cc (H) cc cc (F) c	cc (H) cc cc (F)	Abnormal Not diagnostic	Inf
6	X+− Y− Z−	RAD	LADU	cc (H) cc (F) c	cc (H) cc cc (F) c	LVH	LVH Ant Inf Sept
7	X+− Y−+ Z−	LAD	LPU	c (H) c (F) c	c (H) cc c (F)	RVH	Ant Inf Sept RBBB
8	X− Y− Z−	RAD	RAU	cc (H) cc cc (F)	cc (H) cc cc (F)	LVH	LVH Inf
9	X− Y+ Z−	LAD	RAU	cc (H) cc cc (F)	cc (H) cc cc (F) cc	LVH RBBB	Inf Sept Lat high post RBBB
10	X− Y−	LAD	LAD	cc (H) cc cc (F) cc	cc (H) cc cc (F) cc	LVH	Ant

Key: Tables I-IV. X, Right-to-left axis; Y, A ... axis; Z, Vertical axis. Changes ... [illegible] Y and Z ... X and Z ... Y +. Changes in opposite direction in X, Y and Z. ... Initial forces ... R, L, A, P, U, D, Right, left, anterior, posterior, superior, inferior ... [illegible] QRS. Clockwise, cc, Counterclockwise; H & F, Horizontal, sagittal and frontal projections, respectively ... [illegible] LVH, RVH, Left and right ventricular hypertrophy, respectively; IV block ... block; RBBB, LBBB, Right and left bundle branch block, respectively; ... Ant, Sept, Lat, High post, Inferior, anterior, septal, lateral, and high posterior myocardial infarct, respectively ... [illegible] (each ... = 0.005 second). Angle H ... [illegible] ... When the largest vector ... [illegible] ... positive when superior ... negative

Table II Vectorcardiographic data in Cases 11 19

Case number	Changes X Y Z axes	Orientation of earliest forces		Direction of inscription				VCG Dx	
				Earliest force		Body			
		1st	2nd	1st	2nd	1st	2nd	1st	2nd
11	X− Z−	RAD	RAU	cc (H) cc (F)		8 (H) 8 cc (F) 8		LVH Ant	LVH Ant Inf Lat
12	X− Y− Z−	RAU	RIU	cc (H) (F)		cc (H) (F)		LVH Inf	LVH Ant Inf Sept Lat
13	X− Y−+ Z−	LAD	LPU	cc (H) cc (F) c		cc (H) c cc (F)		LVH Ant Sept	LVH Ant Inf Sept (high post?)
14	X+ Y−	RAD	RAD	cc (H) (F) c		cc (H) cc cc (F) cc		LVH Ant Inf Lat	LVH Ant Inf Sept Lat
15	X− Y− Z−+	RAU	RPU	cc (H) (F)		cc (H) cc 8 (F)		LVH Inf	LVH Ant Inf Sept
16	X+ Y−+	LAU	LPU	cc (H) cc (F)		cc (H) cc (F)		LVH Inf	LVH Ant Inf Sept
17	X−+ Y+ Z−	LAD	RPU	cc (H) cc (F)		8 (H) cc (F)		LVH Ant	LVH Ant Inf Sept Lat Incomplete RBBB
18	X+ Y+ Z	RPD	LPU	(H) cc (F)		8 (H) 8 cc (F) cc		LVH IV block Ant Sept	LVH IV block Ant Inf Sept
19	X− Y− Z−	LAD	RPU	cc (H) cc (F)		cc (H) c 8 (F)		LVH Ant	LVH Ant Inf Sept Lat IV block

For key to table see Table I

clockwise inscription in all of them after infarction In Case 7 with right ventricular hypertrophy the earliest forces displayed clockwise inscription before and after the infarction The initial forces were counterclockwise in Case 10 before and after the occurrence of anterior myocardial infarction

In Cases 12 15 and 16 an anterior wall lesion occurred for the first time with a second clinical episode of infarction The changes diagnostic of anterior infarction were a shift to a posterior position of the body of the QRS in all 3 clockwise inscription of the initial forces in the horizontal projection in Cases 12 and 15 and clockwise inscription of the body of the QRS in the horizontal plane in Case 12

Study of the superimposed tracings shows that the general disposition of the QRS loop beyond the early forces depends largely upon the preinfarction morphology of the loop Striking changes toward the end of the loop did occur however in one case (Fig 6 Case 13) Changes in the terminal loops in the postinfarction vectorcardiograms in Case 7* (Fig 4) and Case 9* are due to the occurrence of right bundle

*QRS duration in these cases increased from ... in pre ... to post ... in ... vectorcardiograms in Case 7 0.0... 115 ... Case 9 0.12 ... 0.13 sec

Table III *Vectorcardiographic data in Cases 1 10*

Case number	Angle in H		Angle in F				Earliest forces (frontal plane) Change from D to U		Duration	Max mil	Sup/Inf ratio	S ep	VCG Dx of infarct
	1st	2nd	1st	2nd	1st	2nd	1st	2nd	2nd	2nd (sec)	2nd	2nd (sec)	
1	− 2	− 4	− 85	− 90	cc D	c U	20	0	12	09	00	29	Inf Ant
2	− 1	−12	− 87	+ 7	cc D	DU	22	7	13	045	1 8	21	Inf Ant Sept
3	0	−12	−109	− 16	cc D	DU	16	9	5	04	00	16	Inf Ant Sept
4	+ 2	− 1	−105	− 98	cc D	c U	18	0	10	21	51	15	Inf Sept
5	+ 8	+ 5	+ 75	+ 60	cc D	U	22	0	11	12	35	07	Inf
6	− 8	− 8	+ 12	+ 8	cc D	c DU	24	5	13	03	30	51	Inf Ant Sept
7	+30	−13	+ 71	+ 43	D	U	23	0	8	05	50	055	Inf Ant Sept
8	−14	−19	+ 18	+ 30	cc D	U	Entirely inferior	0	12	12	24	19	Inf
9	−16	No leftward forces	−105	−115	cc D	U	19	0	24	20	00	06	Inf Sept Lat High post
10	+ 5	−20	+ 69	+ 58	cc D	cc D	—	—	—	—	—	—	Ant

For key to abbreviations see Table I

branch block and in Case 17* to the development of incomplete right bundle branch block. Right bundle branch block, as is well known, alters the terminal portion of the QRS loop. The changes in Case 19* (Fig 5) are associated with the appearance of nonspecific intraventricular block.

Discussion

Diagnostic vectorcardiographic signs of myocardial infarction were observed to appear in association with episodes of clinical myocardial infarction. The technique of superimposition of serial vectorcardiographic loops proved to be eminently useful in demonstrating the diagnostic changes comprising for the most part the earliest superiorly oriented forces in inferior myocardial infarction and increased magnitude of posterior vectors located within 0 045 second after onset of the QRS loop in anterior infarction.

As a result of our previous studies diagnostic importance was attached to orientation and direction of rotation of initial and early QRS forces, rotation of the body of the QRS loop, duration of

*QRS d ... them ... crossed ... of ... ... vect ... card ... gram ... Case 17 ... 00 ... 1 ... ... Case 19 ... 00 ... 0 87 sec

Table IV. Vectorcardiographic data in Cases 11-19

Case number	Angle in II		Angle I				Earliest forces (Frontal plane)										VCG Dx first	
							Change from D to U		Duration		Maximal		Sup./Inf. ratio		Sweep			
	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd (msec.)	1st	2nd	1st	2nd (msec.)	1st	2nd
11	−15	−10	+6	+5	cc D	U	19	0		16		065		1.0		115	Ant	Inf Ant [illegible]
12	−2	0	+22	+32	U	c U	0	0	9	16	09	27	29	6	21	15	Inf	Inf Ant Sept Lat
13	−20	−12	+5	[illegible]	c D	c U	11	0		14		17		1.2		10	Ant Sept	Inf Ant Sept High post?
14	−17	−15	−95	−71	D	D	8	9	8	9	07	11	00	00	25	22	Inf Ant Lat	Inf Ant Sept Lat
15	−3	−5	+22		U	c U	0	0	6	12	08	15	09	15	18	10	Inf	Inf Ant Sept
16	−4	−1	+12	+28	U	U	0	0	6	6	06	01	16	05	13	07	Inf	Inf Ant Sept
17	−20	−1	−15	+65	c D	c U	16	0		15		1		59		24	Ant	Inf Ant Sept, Lat
18	−30	−9	+4	−95	D	c U	24	0	0	26+		10		00		11	Ant Sept	Inf Ant Sept
19	−13	−11	+36	−15	cc D	c U	Entirely inferior	0		11		09		2.1		16	Ant	Inf Ant Sept Lat

For symbols see Table I.

superior forces and magnitude of superior and posterior vectors The magnitude of certain vectors may be the only distinction between the noninfarct vectorcardiogram and that of anterior and posterior myocardial infarction Superimposition of serial vectorcardiograms a method of demonstrating vectorcardiographic changes not previously exploited has emphasized the validity of these empirical diagnostic features Such an apparently trivial feature as clockwise inscription of initial forces has acquired greater diagnostic validity by the demonstration of its appearance during a clinical episode of acute myocardial infarction This is also true of the other diagnostic features discussed above The superimposition technique thus helps to validate these diagnostic features of infarction of the myocardium In some cases of second infarct the only change is in the magnitude of the abnormal vectors and the vectorcardiographic diagnosis of recurrent infarction can be made best by the superimposition technique

The *time of change* from inferior to superior orientation of initial forces has been shown to be a reliable sign of inferior infarction However the change in orientation may not begin at the 0 *point but at* a variable time interval beyond it a pattern which is also observed *in noninfarct* vectorcardiograms It is noteworthy that prior to the occurrence of infarction the briefest *interval from the onset of* ventricular depolarization to reversal from *inferior* to superior orientation is 0 04 second and that after the development of *inferior* infarction the longest corresponding interval is 0 02 second Vectors which change to superior orientation later than 0 02 second after the 0 point are not classified as earliest forces and are *not* diagnostic of infarction

It is generally agreed that diagnostic signs of myocardial infarction are located in the early depolarization *forces and* our data clearly confirm this opinion However changes in the later or *terminal* portion of the depolarization loop have been observed and it has been suggested that diagnostic signs may be found in this part of the vectorcardiogram Striking changes in this portion of the vectorcardiogram were observed in one of our cases in which the question of high posterior infarct was raised Such a lesion located in the posturobasal region of the left ventricle would affect the terminal portion of the QRS loop if this region were the last fraction of myocardium to be depolarized Changes in other cases were associated with the development of intraventricular block or were minor and not significant for the following reasons (1) There is a certain amount of variability from day to day and even from loop to loop at the same recording (2) The configuration of the terminal portion is to some extent conditioned by the earlier vector (3) Myocardial infarction affects the S T junction Thus the changes which occur in the terminal portion of the loop may indeed be the result of infarction but in our experience do not help in diagnosis and localization

Summary and conclusions

1 The diagnostic signs of myocardial infarction were studied by *superimposition* of vectorcardiograms obtained before and after a first myocardial infarction and before and after a second myocardial infarction

2 These studies confirm the view that diagnostic signs of infarction occur in the initial and or early portion of the depolarization loop Configuration of the rest of the body of the loop and the terminal appendage is largely determined by the preinfarction morphology of the loop

3 Signs in use in this laboratory for the diagnosis of anterior and inferior myocardial infarction have been shown to appear for the first time in association with clinical acute myocardial infarction

4 The diagnostic signs of anterior myocardial infarction are increased posterior displacement early in the QRS loop displacement of the body of the QRS loop to a posterior position change from counterclockwise to clockwise inscription of the initial forces and the body of the QRS loop in the horizontal projection and concavity of the centrifugal limb of the QRS loop

5 The diagnostic signs of inferior myocardial infarction are confined to the initial or early depolarization forces and consist in superior orientation clockwise inscription abnormal magnitude and greater than

normal duration abnormally wide sweep and greater than normal superior inferior ratio

6 Vectorcardiographic signs of infarction in multiple areas may occur in association with a single clinical episode of acute myocardial infarction

7 Pre-existing signs of myocardial infarction may become less conspicuous after the occurrence of a second myocardial infarction When the second infarct is in the same location as the first one the magnitude of the diagnostic signs increases

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Partial rupture of pulmonary artery with lesions of medionecrosis in a case of mitral stenosis

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Initially idiopathic medionecrosis was considered to be a local disease of the aorta at the point at which a dissecting aneurysm or a spontaneous rupture had developed (Erdheim Gsell) Later on it was interpreted to be a systemic disease of the elastic arteries (Wolff) Our own findings in two cases of spontaneous partial rupture of the aorta where severe lesions were also observed in peripheral vessels led us to believe that medionecrosis is in fact a systemic arterial disease which may attack mainly arteries of the pulmonary circulation as shown by the case we are describing

Looking through the cases which have been reported in previous publications we find that the macroscopic and microscopic aspects of idiopathic medionecrosis i e dissecting aneurysm and spontaneous rupture and destruction of the elastic tissue necrosis of the muscle fibers without reaction increase of the basophilic ground substance vascularization of the media etc as described for the aorta are also found in the pulmonary artery although such localization is fa less frequent

Case report

C M M 27 year-old single woman was hospitalized on account of dyspnea and edema of the lower limbs The patient had had rheumatic fever at the age of 14 ears with recurrences at 15 and 16 Since her eighteenth birthday the patient had been suffering from dyspnea on exertion reaching the point of orthopnea sometimes producing foamy and reddish-colored sputum There were tw report of hemorrhages Nocturi and edema of the lower limbs had increased during the last months

Clinical examination Cyanosi red pots on the cheek and moderat dyspnea ere observed The blood pressure was 100/72 mm Hg The objective examination revealed two diastolic murmur and opening snap t the apex strong systolic-diastolic murmur (Graham Steell) t the pulmonary focu and pronounced sta is of the lungs The liver was enlarged The lower limbs showed edema

X ray examination The heart was enlarged due to the size of the right entricle and left trium The pulmonary artery showed enormous dilation Advanced interstitial sclerosi nd hemosiderosic nodules were observed

Electrocardiogram Marked hypertrophy and overload of the right entricle could be demonstrated

The patient showed slight improvement after treatment with cardiac timulants and diuretic There were still signs of cyanosi dyspnea and subedema of the lung after exertion Surgical intervention was suggested for valvulotomy During the operation carried out on Nov 27 1954 th good results from the al ulotom the cyanosis increased pontaneous breathing was not restored and the patient died from respiratory insufficiency with cyanosis nd com

Postmortem diagnosis The diagnoses were old endocarditi at the mitral alv th tenosi dilatation of the left atrium pulmonary therosclerosis partial rupture of the pulmonary artery at the posterior all dilatation of the right cardiac ca ities and right entricular hypertrophy and congestion of the internal organs

Macroscop p a of the pulmonary artery Tw centimeters abo the pulmonary alv the posterior wall showed trans erse tear (Fig 1)

From th Instit d Anat mia P tológica da F culd d d Medicina de Lisboa Lisbon Portugal
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Fig 1 Partial rupture of the main pulmonary arterial trunk Macroscopic pect



Fig 2 Tran erse laceration of the trunk and right branch of the pulmonary artery Macroscopic pect

which extended into the right branch (Fig 2) The lesion was 11 cm long and 3 cm high The edges round and protruding t the level of the trunk, flattened out toward the di tal part of the tear until they reached more or less the same level as the remaining wall of the artery Near the rupture the intima was of tran lucent and shiny bluish gray color Further away from the lacerated part there were some depressed blui h-gray areas in the intima and lipoid plaques All the arterial branches showed diffuse dilatation

Histologic examination of the pulmonary artery The lesion con isted of a break in the intima nd media which extended three quarters of the way through the media (Fig 3) At this point of the artery the wall was formed by a dense connectiv ti sue and capillaries which were sometimes obviou ly engorged (Fig 4) without any smooth muscle fibers or elastic laminae Only a few of the elastic laminae of the outer layer of the media could be found I the peripheral area nearer the edges of the laceration w did find some mooth muscle fibers and elastic laminae The appearance of the medial break aried In places the edge of the tear was round Elsewhere t was sharp (Fig 5) Some elastic fibers extended to the margin of the break Other fibers were thinned and did not qu t reach the margin of the laceration (Weigert elastic ti ue tai) I timal ti ue covered the edges and passed int the connectiv tissue of the tear

The remaining part of the essel wall howed some eosinophilic necrotic foci containing no nuclei several areas w thout ela tic fibers (Fig 6) and a *focal increase of basophilic metachrom tic* and PAS-negative ground bst nce Because of the increase in thi ubstance wider distances between the fibers or formation of small cy tic ca ities were seen (Fig 7) Vasa asorum may ha reached the



Fig 3 Interruption of the intima nd med Lacer tion (Hematoxylin and eosin stain)

medial third of the media The intima was thickened especially in the area in which elastic laminae showed the most intense destruction Muscle fibers may hav participated in the formation of the thickened areas The adventitia was thickened and partly hyalinized

The depressed area seen macroscopically corresponded to large medial focus without elastic laminae covered by a strand of connective tissue which extended into the intima

Intrapulmonary artery There was intense thickening of the intima which contained some foamy cells t several places a newly formed internal elastic membrane was outlined

Aorta N p thologi findings ere observed n the aorta

Discussion

The foregoing description shows that there were severe lesions of chronic medionecrosis (in the sense of Farr[4]) with one of the main characteristics being the destruction of the elastic laminae Because of this destruction a partial rupture of the artery developed Proof of the long standing process was the presence of fibrous scar tissue filling the gap of the laceration In the depressed area seen macroscopically this scar tissue was situated on the same level as the remainder of the media Another finding which indicated the age of the lesion w is the scarcity of recent necrotic foci Vascularization of the media thickening of the intima and the adventitia are further alterations usually found in vessels with medionecrosis Signs of regeneration of muscle fibers or elastic laminae sometimes referred to in cases of medionecrosis [3,4] were absent The alterations of the pulmonary arteries were due to pulmonary hypertension

On the assumption that the dissecting aneurysm and the spontaneous rupture are the results of the same pathologic process i e medionecrosis we collected 42 cases (including our own) described in the literature (Table I) Tables II and III show the most important clinical and pathologic findings We consider this classification to have better morphologic foundations than the definition of spontaneous rupture of the pulmonary art ry defended by Brettell[1] and McNaught as a separate disease

We should like to draw attention to the case de cribed by Duffield in which a dissecting aneurysm and a spontaneous rupture existed simultaneously in the right



Fig 4 Important vascularization of the fibrous scar tissue t the tear of the media (Hematoxylin and eosin stain)



Fig 5 Sharp edge of the tear D struction of the elastic laminae (Weigert el tic tissue



Fig. 6. Foci of the media without elastic laminae outside the lacerated area, seen macroscopically. (Weigert elastic tissue stain.)



Fig. 7. Focus of increased ground substance outside the laceration. (Hematoxylin and eosin stain.)

and left pulmonary arteries. This case confirms our opinion as shown in Table I.

Landert[23] described the case of a patient with a dissecting aneurysm of the aorta and at the same time a spontaneous rupture of the left branch of the pulmonary artery. Of course, this coexistence may be due to mere coincidence.

The case presented by Fowler is doubtful, since the diagnosis was based on nothing but clinical symptoms, which are insufficient for the recognition of this disease.[17] The rupture was a hypothesis offered by the physician to explain the sudden death.

Medionecrosis of the pulmonary artery is a rare disease with no marked preference for either sex, contrary to the findings with medionecrosis of the aorta.[8, 14] The same difference exists between the aneurysm of the pulmonary arteries and that of the aorta.[7] Medionecrosis of the pulmonary artery occurs most frequently between the ages of 20 and 29 and 40 and 49 years. In the majority of cases the macroscopic lesion is found in the main trunk, followed in frequency by the right branch. The number of cases which show a real aneurysm is far surpassed by the number in which it is absent. Saccular aneurysms are more frequent than the spindle-form variety. *Cases in which there is extensive* thrombosis are very seldom met with.[14]

Comparing medionecrosis of the pulmonary artery with aneurysm of the same vessel, we find that the latter is also very rare,[11, 29 ... 31, 33] although much more frequent

Table I. Cases of medionecrosis

Dissecting aneurysm (total 15 cases)	
With internal tear	7
Without internal tear	2
With aneurysm	3
Without aneurysm	8
Spontaneous rupture (total 27 cases)	
Total rupture	
With aneurysm	11
Without aneurysm	4
Partial rupture	
With aneurysm	2
Without aneurysm	3

than medionecrosis of the pulmonary artery. It shows no predilection for either sex,[3, 7] is localized mostly in the main trunk,[2, 3] and is described predominantly as saccular[18] or spindle shaped.[4, 7] Only by systematic microscopic examination will it be possible to decide whether there is indeed a closer relation between the aneurysm of the pulmonary artery and medionecrosis.

The symptoms vary and depend on the primary disease. Sudden precordial, substernal, or thoracic pain reported in a certain number of cases and occasionally combined with anguish seems to correspond to the rupture. Radiation of the pain into the arms may be present. In one case the radiation of pain into the right arm was related to the rupture of the right branch of the pulmonary artery. Collapse, state of shock, and sudden death are due to the ensuing hemorrhage. In most cases there is a total rupture of the wall with lethal hemorrhage, especially into the pericardium (Table IV).

Two out of 7 cases without rupture are cases of dissecting aneurysms. The other cases—like the one we observed—can be considered to be partial ruptures. The explanation for the fact that partial rupture seems to be relatively rare is that it does not cause death. When death occurs it is due to concomitant diseases, endocarditis caused by streptococcus infection,[26] and after effects of surgical intervention.[27] Finally, partial ruptures may be incidental postmortem findings. Thus, cases may be easily overlooked, probably because of a lack of histologic examination.

The microscopic lesions—rarely reported—correspond to those of medionecrosis.[1, 21, 22, 31] From this point of view our case is rather instructive.

We disagree with Brettell,[14] who considers the microscopic findings in cases of spontaneous rupture of the pulmonary artery to be similar to those described in aging. We think that there are marked differences between our Fig. 5, for instance, and the findings of Heath,[34] who dealt with the structure of the pulmonary artery at different ages.

The different primary diseases reported in cases of medionecrosis of the pulmonary artery are indicated in Table V. All of them are the consequences of pulmonary hypertension. Among the cases of hypertension caused by congenital abnormalities we rather frequently find cases of patent ductus arteriosus. Among those due to acquired pulmonary hypertension, mitral stenosis ranks first. Morphologic findings of pulmonary hypertension such as hypertrophy of the right ventricle and/or pulmonary atherosclerosis were found in 26 cases. In the others these alterations cannot be excluded because the case reports are not always sufficiently detailed. The pathogenic factors considered were bacterial infection,[8] syphilis, chronic deforming inflammation,[4] rheumatism,[4, 1] trauma,[17] atherosclerosis, and pulmonary hypertension.[3, 17, 1] Other authors mention hypoplasia[19] or congenital abnormalities[1, 4] as responsible factors. We should like to point out that the same factors are considered to be responsible for the aneurysm of the pulmonary artery.[1, 18, 37]

With regard to medionecrosis of the pulmonary artery the above mentioned pathologic situations cannot be considered as being all etiological factors. Some of them, such as trauma, syphilis, rheumatism, and bacterial infection, do not have sufficient foundation and are by no means constant. Endocarditis as mentioned in the Hartwell case[23] may have played some part in the start of the rupture, but there is reason to doubt that it was the only cause. In one of the cases thought to be due to syphilis the author himself (Neuburger[8]) stressed that the Wassermann reaction was negative and that nothing in the case history could be found to point to syphilis. Atherosclerosis can be considered to be a consequence of the existing pulmonary hypertension rather than a cause of medionecrosis.

The hypertension, which is practically constant in cases of medionecrosis of the pulmonary artery, has undoubtedly an important part as an etiologic factor, perhaps even more so than in cases of medionecrosis of the aorta,[38] at least in respect to the localization. The fact that congenital heart disease is found in a relatively large number of cases of medionecrosis might suggest—as an analogy to medionecrosis of the aorta—that there is a congenital weakness of the vascular wall[39, 34] wh

Table II. Dissecting aneurysms

Author	Age (yr.)	Sex	Primary disease	Localization	Aneurysm	Intimal tear
Helmbrecht 1842 (cited by Posselt)	21	M	Pulmonary hypertension	Main trunk		+
Tonze 1863 (cited by Posselt)	49	M		Main trunk	–	
Duffield 1882	50	F	Pulmonary emphysema	Right branch	+	
Vincenzo 1904	25	M	Congenital mitral stenosis	Main trunk	Saccular	+
Neuburger 1930	28	F	Pulmonary tuberculosis emphysema	Main trunk	–	+
McNaught[19] 1935	44	F	Mitral and tricuspid stenosis with insufficiency	Main trunk		+
Lanbly and Routier[illegible] 1941	47	M	Defect of interauricular septa	Main trunk	Spindle shaped	
Foord[illegible] 1947	26	F	Patent ductus arteriosus	Main trunk, right branch	–	–
	70	M	Pulmonary tuberculosis emphysema	Right branch	–	–
Crampton 19[illegible]0	19	M	Common truncus arteriosus with 3 valves, interventricular septal defect, hypoplasia of the aorta (Humphrey type 4)	Main trunk and branches	–	+
Obela and Teir 1954 (cited by Brettell[illegible])	61	M				
	31	M	Cardiac congenital disease, patent ductus arteriosus			
Fleming[illegible] 1956	26	M	Common truncus arteriosus, patent ductus arteriosus	Main trunk	–	+
Odinokowa 1956 (cited by Foord[illegible])	43	F	Mitral stenosis	Main trunk	–	
Durno and Brown[illegible] 1908	33	M	Patent ductus arteriosus	Main trunk	–	+

Athero sclerosis	*RVH*	*External rupture*	*Interpretation*	*Microscopic finding*
+		Hemopericardium	Pulmonary hypertension	—
		+		
+	+	Hemopericardium		
+	+	Hemopericardium	Pulmonary hypertension congenital abnormality syphilis	Muscle fibers destroyed irregularities of elastic fibers vasa vasorum obliterated
	+	Hemopericardium	Syphilis hypertension congenital abnormality	
+	+	Hemopericardium		Increased mucoid material elastic fiber farther part and fragmented muscle fibers decreased in amount increase of fibrous tissue
+	+		Atherosclerosis congenital abnormality	
+		Mediastinum		Elastic laminae and muscle fibers destroyed increased ground substance
		Lung		
				Intima enlarged irregularities of the elastic fibers blood between the connective fibers
				Degeneration of the media
+	+	Hemopericardium	Similar to the idiopathic medionecrosis of the aorta	Elastic and muscle fibers destroyed increased ground substance
	+	Hemopericardium	Rheumatism	
+	+	Hemopericardium		

Table III *Spontaneous ruptures*

Author	*Age (yr)*	*Sex*	*P mary disease*	*Local zation*	*Aneurysm*
Dla h 1846 (cited by Posselt[4])	22	M	Mitral stenosis	Main trunk	Saccular
Dow 1847	19	F	Rheumatism	Main trunk	+
Duffield 1882	50	F	Pulmonary emphysema	Left branch	Saccular
Posselt 1896	45	F	M tral stenosis	Right branch	–
Stoerch 1899 (cited by Po elt[4])	20	F	Small orta several ectasias of the pulmonary artery	Left branch	–
Loveland 1901	41	M	Chronic adhesi pericarditis mitral insufficiency	Right branch	Saccular
Mantovan 1902 (cited by Boyd)	75	M	M tral steno congenital pulmonary stenosis	Main trunk	Spindle shaped
Po selt 1909	45	F	M tral stenosis nd insufficiency	Right branch	
Arrilago 1924	38	M		Main trunk	Saccular
Moench 1924	42	F	Bicuspid pulmonary al e patent ductus arteriosus	M trunk	+
F orte 1934	18	M	Subtype of cor biatri m triloculare w th hypo pla ia and dextroposition of aorta	Ma trunk	–
Fowler[a] 1936	59	M		Main trunk	
Duperne and La chaud[b] 1939	44	F	Congestiv heart f ilure pulmonary athero sclerosis therosclerosis	Ma tru k	Spindle shaped
Longland[c] 1943	68	M	Atheroscleros s therosclerotic nephrosclerosis	Main trunk	–
Y nks[d] 1943	21	F	Patent *ductus art riosus*	Right branch	Saccular
Hartwell and Til den[e] 1943	12	F	P tent ductus arterio bacut staphylo coccic endocard tis	Main trunk	Saccula
Deterling[f] 1947	37	M	Patent ductus arteriosus	Right branch	+
Lindert[g] 1950	67	F	Patent ductus arteriosus dissecting aneurysm of aorta	Left branch	–
Obela nd Terr[h] 1954 (cited by Brettell[i])	72	F			
Thomas et al 1955	42	F	Mitral stenosis	Main trunk	–
Madeloff 1956 (cited by Brettell[14])	56	F	Mitral tenosis	Main trunk	

Athero sclerosis	*RVH*	*External rupture*	*Interpretation*	*Microscopic findings*
+	+	Hemopericardium		
+	+	Hemopericardium		
+	+	Hemopericardium		
+	+	–		
+		Bronchus	Chronic deforming inflammation	
+		Hemothorax		
		+	Rheumatism congenital abnormality	
+		–		
+		Hemopericardium	Atherosclerosis	
		Hemopericardium		
		Hemopericardium	Pulmonary hypertension	Elastic laminae farther apart and fragmented
		+		
+	+	Hemopericardium	Atherosclerosis	
		Hemopericardium	Hypoplasia	Pycnotic nuclei
		Bronchus	Congenital abnormality	
		–	Congenital abnormality bacterial infection	
+	+	–	Atherosclerosis patent duct arteriosus trauma	
		Anterior mediastinum		
				Intimal thickening irregularities of elastic fibers blood between connective fibers
+	+	Hemopericardium	Pulmonary hypertension	Elastic laminae destroyed increased ground substance thickening of intima and adventitia sclerosis of vasa vasorum
+				Without degeneration of media

Table III Spontaneous ruptures—Cont'd

Author	*Age (yr)*	*Sex*	*Primary disease*	*Localization*	*Aneurysm*
Kodolov 1956 (cited by Brettell[14])	40	M	Mitral stenosis	Left branch	
Condry[50] 1958	61	M	Pulmonary emphysema	Main trunk	–
Brettell[14] 1960	66	F	Pulmonary hypertension due to thrombosis and embolism	Main trunk	–
	60	F	Pulmonary hypertension (asthma)	Main trunk	–
Rain 1960 (cited by Brettell[14])	27	M	Idiopathic pulmonary hypertension	Main trunk left and right branches	+
Levy 1960	27	F	Mitral stenosis	Main trunk right branch	—

Table IV External rupture of aneurysms

Ruptured site	*Number of cases*
Pericardium	18
Mediastinum	2
Bronchus	2
Pleura	1
Lung	1

Table V Primary disease in cases of medionecrosis of pulmonary artery

Primary disease	*Number of cases*
Congenital pulmonary hypertension	
Patent ductus arteriosus	6
Mitral stenosis	2
Interauricular septal defect	1
Pulmonary stenosis	1
Patent ductus arteriosus bicuspid pulmonary valve	1
Subtype of cor triloculare	1
Common truncus arteriosus with 3 valves interventricular septal defect, hypoplasia of aorta	1
Acquired pulmonary hypertension	
Mitral stenosis	10
Pulmonary tuberculosis	2
Emphysema	1
Thrombosis and embolism	1
Asthma	1
Without known cause	3

exist in cases of acquired pulmonary hypertension However considering the experimental results (medionecrosis caused experimentally in rabbits by collapse) and data from human pathology (medionecrosis of the human aorta after shock) (Faria[9,48]) one is led to think that lack of oxygen may be an important factor The deficient supply of oxygen may be brought about *indirectly by pulmonary hypertension and* may be responsible—at least in part—for the medionecrosis since obstruction of the vasa vasorum mentioned by some authors as a cause of medionecrosis of the aorta[11,49] is in fact not a constant finding[1,2,48,50]

We hope that systematic studies of the pulmonary artery carried out in future research will provide evidence for our theory

Summary

There are macroscopic and microscopic aspects of medionecrosis of the pulmonary artery which are in line with those described for medionecrosis of the aorta

Fifteen cases of dissecting aneurysms and 27 cases of spontaneous rupture of the pulmonary artery have been considered including one case observed by the author This case had certain peculiarities which had not been described before—partial rupture of the trunk of the pulmonary artery with severe medionecrosis occurring

Athero-sclerosis	RVH	External rupture	Interpretation	Microscopic findings
				Degeneration of media ela tic fibers fragmented
+	+	Hemopericardium	Atherosclerosis	
+	+	Hemopericardium	Pulmonary hypertension	Increased basophilic substance connective fibers of media fragmented
+	+	Hemopericardium	Pulmonary hypertension	Increased basophilic substance
		+		Hyalinization of the intim local destruc tion of elastic fibers necrosis t the rupture
+	+	−	Anoxia	Destruction of elastic and muscles fibers ncreased ground substance thickening of intima nd ad entitia

in a case of mitral stenosis The patient died during surgical intervention

The etiology and pathogenesis of medio necrosis of the pulmonary artery are dis cussed The importance of pulmonary hyper tension and lack of oxygen are pointed out

Medionecrosis is considered to be an aortic disease of the arteries affecting vessels of the pulmonary and aortic circulation

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Initial myocardial infarction among veterans
Nontransmural myocardial infarction
Bundle branch block

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In a previous study of initial myocardial infarction a group of patients was described whose electrocardiograms were typical of transmural infarction. There was an additional group of patients who were treated for their first myocardial infarction but who did not have diagnostic electrocardiographic changes. The electrocardiograms of these patients showed either bundle branch block or only S-T segment and T wave changes compatible with a nontransmural myocardial infarction. These patients are reported separately because they represent a poorly defined entity about which less is known.

Selection of study cases

Review was made of records of men discharged with the diagnosis of coronary artery disease from 33 large teaching Veterans Administration Hospitals during the years 1950 to 1952. The records of 631 patients who had had a first myocardial infarction were selected. The details of the sampling technique and criteria of selection were reported in a previous publication.

The 631 cases were subdivided into three groups on the basis of the electrocardiographic findings: (1) transmural infarction—512 cases or 81 per cent, (2) nontransmural infarction—96 cases or 15 per cent, and (3) persistent bundle branch block—23 cases or 4 per cent of the total acceptable group. The transmural group was analyzed and reported on in a previous paper.

Nontransmural myocardial infarction

Two of the original 96 cases of nontransmural infarction were discarded from the study because further review of the electrocardiograms revealed significant Q waves. The electrocardiograms in the other 94 cases were not pathognomonic of an acute myocardial infarction. The clinical picture together with such evidences of myocardial necrosis as fever, elevated erythrocyte sedimentation rate, leukocytosis, and serial electrocardiographic changes were used in establishing the diagnosis.

Description of clinical findings and comparison with transmural group

Age. The age distribution was determined by the method of selection. Twenty-nine (30 per cent) of the 94 patients were under 50 years of age at the time of onset of their

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myocardial infarction and 65 (70 per cent) were 50 years or older Table I compares the age distribution with that of the previously reported group with transmural myocardial infarction

History of hypertension and angina pectoris There was a history of hypertension in 31 per cent of the patients of this group as compared to only 19 per cent in the transmural group (Table I) A history of angina pectoris was found in approximately the same percentage of patients as in the group with transmural infarction

History of pain Eighty nine patients had an episode of pain characteristic of myocardial infarction The other 5 patients had frequent intermittent episodes of pain The duration of pain is shown in Table I The incidence of hemorrhage shock vigorous exertion or operation in the immediate preinfarction period was the same in both groups

Electrocardiographic findings Re examination of the electrocardiograms for the purpose of detailed analysis of the S-T segment and T waves was possible in all but one of this group All had electrocardiograms showing abnormalities of either the S T segment or T wave or both none showed abnormal Q waves Six patients had a single electrocardiogram 5 of these died during the hospital period In all of the other patients either T wave abnormalities or S T segment abnormalities or both were present in more than one tracing The electrocardiograms of 2 patients showed only S-T segment deviations One of these patients died on the second hospital day and had only one electrocardiogram The other patient exhibited S T segment abnormalities in multiple leads in several tracings T wave abnormalities without associated abnormal S-T segments were seen in the electrocardiograms of 13 patients

Clinical course and laboratory findings The clinical course and laboratory findings in the two groups differed in certain categories (Table I) There was a higher incidence of shock and leukocytosis in the transmural group Only 2 per cent of the patients in the nontransmural group had an oral temperature of greater than 101 F for 3 days or more during the first week as compared to 10 per cent of the patients in the transmural group There was no significant difference in the incidence of abnormal rhythms nor of congestive heart failure in the two groups

There were two definite instances and one questionable one of thromboembolic complications Eleven patients developed typical electrocardiographic evidence of transmural myocardial infarctions during the hospital period These electrocardiographic changes represented either a second myocardial infarction or a definite extension of the original nontransmural infarction In each of the 11 patients there was an associated clinical event characterized by some or all of the following recurrent episode of pain shock fever leukocytosis or increase in the erythrocyte sedimentation rate These transmural infarctions occurred during the first week after the original event in 3 patients during the second week in 4 patients and during the third week or later in 4 patients Three of the 11 patients who developed a transmural infarction died during the first 2 months

Anticoagulant therapy Sixty five (69 per cent) of the patients received anticoagulant therapy but in 6 patients the dosage used or the duration of therapy was inadequate for any therapeutic benefit Seven of the 11 patients who developed a transmural infarction were receiving anticoagulant therapy at the time of the event The 2 patients with a definite thromboembolic complication had not received anticoagulant therapy Three patients had minor episodes of hemorrhage one of these had not received anticoagulant therapy

Immediate and five year mortality

The integrated records system of the Veterans Administration provided survival data on all patients without direct communication with a veteran or his family The deaths during the first 2 months after onset of the acute myocardial infarction are referred to as the immediate fatalities Those patients who did not die during the first 2 months are referred to as survivors or recovered patients

Twelve (13 per cent) of the 94 patients died during the initial 2 month period Of these 12 patients 7 died during the first week 3 during the second week and one each in the third and fourth weeks Twenty one (26 per cent) of the 82 survi

Table I Comparison of nontransmural group with previously reported transmural group

	94 Nontransmural Total number	94 Nontransmural Per cent	503 Transmural (per cent)
Age			
Under 40	7	8	15
40–49	22	23	21
50–59	44	47	42
60–69	18	19	17
70 or over	3	3	5
Interval between onset and admission			
In hospital	4	4	3
Less than 24 hr	66	0	62
25–48 hr	13	14	17
49–72 hr	6	7	9
73–96 hr	5	5	9
History of hypertension			
No	53	56	69
Yes	29	31	19
Unknown	12	13	12
Angina pectoris and duration			
No	29	31	35
Unknown	7	7	5
Yes	58	6	60
Less than 1 mo	27	38	50
1 12 mo	13	22	24
1–4 yr	16	28	14
5 yr and over	7	12	11

vors died within 5 years This ratio is referred to as the 5 year mortality rate among recovered patients

This present group of patients had a prognosis similar to that of the previously reported transmural group The differences in immediate mortality rates and in the 5 year mortality rates of survivors of the two groups are not statistically significant (Table II) Fig 1 illustrates the 5 year survival curves of patients over 50 years of age in each group

Table III presents comparisons between the expected and the observed annual mortality rates for the survivors in the two groups The expected annual mortality rates are based upon the 1953 life tables for the white male population of the United States The difference between the expected and observed annual mortality rates is expressed as the excess mortality rate per annum The excess mortality rate of patients over 50 years of age was similar in both groups

The number of patients in this study is too small for detailed analysis of the influence of the individual factors in the past history and clinical course on the mortality rates Twenty patients did not have shock temperature of 99 5°F or more erythrocyte sedimentation rate of 20 mm per hour or more or leukocytosis of 15 000 c ml or more during the first week In spite of the lack of any of the commonly used criteria of myocardial necrosis the prognosis in this group did not differ significantly from that in the remainder of the study group Two patients of this group died one on the day of onset and the other on the nineteenth day after onset of infarction Four of the 18 survivors died in the next 5 years

Table I Comparison of nontransmural with transmural group—Cont d

	94 Nontransmural Total number	94 Nontransmural Per cent	503 Transmural (per cent)
Hemorrhage shock vigorous exertion or operation prior to onset			
No	86	92	93
Yes	8	8	7
Duration of pain (of infarct)			
Not specified	22	24	15
Less than 6 hr	39	41	35
6 hr or longer	33	35	50
Shock (systolic pressure of 90 mm Hg or below)			
No	89	95	87
Yes	5	5	13
Digitalis therapy			
No	84	89	83
Yes	9	10	17
Questionable	1	1	0
Presence of leukocytosis in first week			
Less than 15 000	72	77	64
15 000 or more	19	20	32
Not recorded	3	3	4
Significant arrhythmias			
No	86	91	88
Yes	8	9	12



Fig 1 Comparison of survivorship patients with transmural and nontransmural infarction 50 years of age and over

Autopsy findings in patients dying with nontransmural infarction

Autopsy protocols were available on 8 of the 12 patients who died during the first 2 months and on 7 patients who died during subsequent hospitalizations The coronary arteries were not described in one protocol Severe coronary artery sclerosis with or without occlusion was described in all others The gross and microscopic appearance in each autopsy corresponded well with the clinical age of the infarction Neither hemopericardium nor myocardial rupture was found No evidence of thromboembolic complications was reported in the autopsy findings A brief description of each case follows

Patients dying during first 2 months

CASE I C S died on the day of infarction An area of tan muscle distal to an occlusion of the circumflex branch of the left coronary artery was described The heart weighed 430 grams

CASE II F P died on the second day after onset of infarction Microscopic examination of an area in the posterior wall of the left ventricle showed disintegrating nuclei The heart weighed 300 grams

CASE III H L died on the second day after infarction An area of infarction in the anterior wall was noted but was not well described as to extent There were also scattered areas of fibrosis The heart weighed 450 grams

CASE IV J M died on the second day after infarction A small anterior infarction was fairly well described but the extent was not stated The heart weighed 400 grams

CASE V R C died on the seventh day after onset of pain There was no gross description of the infarction but on microscopic examination areas of fibrosis were described but not localized The heart weighed 450 grams

CASE VI A G died on the ninth day after infarction An area of softening near the junction of the anterior wall and septum was described The heart weighed 500 grams

CASE VII W P died on the nineteenth day after onset of infarction A large transmural infarction involving the anterior wall of the left ventricle and septum was found It was known from the record that this infarction had become transmural during the second week of hospitalization The heart weighed 500 grams

CASE VIII C W died on the twenty seventh day after onset of infarction An anterior infarction near the septum was present From the description this appeared to be subepicardial The heart weighed 480 grams

Patients dying during subsequent hospitalization

CASE I J G died 8 months after his initial myocardial infarction Scattered areas of fibrosis in the left ventricle were described The heart weighed 475 grams

CASE II W R died from carcinoma of the lung about 1 year after his first infarction An old infarction was well described This infarction had become transmural in his sixth hospital week and at autopsy 1 year later a cardiac aneurysm was described The heart weighed 300 grams

CASE III F L died from a second myocardial infarction which occurred 1 year after his first infarction Scarring from an old infarction was described but was not well localized The heart weighed 500 grams

CASE IV J M died 3 years after his first infarction Areas of fibrosis were described but not localized The heart weighed 400 grams

CASE V E A died 3 years after his first infarction An area of old posterior infarction was mentioned but not well described The heart weighed 550 grams

CASE VI P F died from carcinoma of the stomach in 1954 about 4 years after his first infarction Scattered areas of fibrosis in the anterior myocardium were described at autopsy but the size of these areas was not mentioned in the protocol The heart weighed 280 grams

CASE VII A F died from spinal cord tumor 7 years after his initial infarction On microscopic examination an area of fibrous replacement of the myocardium was described but the extent was not stated The heart weighed 385 grams

Discussion

Exact diagnosis of various syndromes associated with ischemia of the myocardium is difficult or impossible in many cases This is particularly true of those patients in whom cardiac pain is of intermediate or long duration and is unaccompanied by the classic electrocardiographic picture of a transmural myocardial infarction The term *transmural infarction* is generally used for those cases in which definitely abnormal Q waves develop in association with the other electrocardiographic changes of myocardial infarction [3]

The patients described in this paper are

in the group in which diagnosis is difficult. A variety of diagnostic terms have been used to describe the cases of this group. Among these are subendocardial infarction, coronary failure,[3,4] acute coronary insufficiency,[4] intermediate coronary syndrome, prodromal symptoms in myocardial infarction,[4] impending myocardial infarction,[5] intramural myocardial infarction, and nontransmural myocardial infarction.[6] It is obvious from the number of terms used that none has proved to be satisfactory. *Subendocardial infarction* perhaps has received the widest usage for those cases in which there is associated laboratory or clinical evidences of myocardial necrosis. This term is not entirely satisfactory because it implies an accurate anatomic location which is not supported either by experimentally produced myocardial lesions[7] or by autopsy study of naturally occurring myocardial infarctions,[8] unless the subendocardial area is defined as all of the heart excluding only the outer one third or subepicardial area. Furthermore, following the classic experiments of Wilson and co-workers,[9] the term *subendocardial infarction* has also been widely used to include cases of myocardial infarction with definitely abnormal QR complexes.

The incidence of laboratory evidence suggestive of myocardial necrosis, the high mortality rate, and the consistency with which anatomic changes were found at

Table II. Comparison of mortality of nontransmural group with that of previously reported transmural group

Type of patient	Number of patients	Deaths in first 2 mo		5 year mortality rate among recovered patients		
		Number	Immediate fatality rate/100	Number of patients	Number of deaths	Rate/100
Nontransmural						
Under 50	29	3	10	26	2	8
50 and over	65	9	14	56	19	34
Transmural						
Under 50	183	20	11	163	36	22
50 and over	320	56	18	264	97	37

Table III. Average excess annual mortality rates among recovered patients during 5 year period after initial myocardial infarction, by age group

Age group	Observed average annual mortality rate per 100 recovered patients†				Expected average annual mortality rate per 100 recovered patients‡	Average excess annual mortality rate per 100 recovered patients	
	Transmural		Nontransmural			Transmural	Nontransmural
40–49	(94§)	4 9	(19§)	1 1	0 7	4 2	0 4
50–59	(182)	1	(36)	6 1	1 9	5 2	4 2
60–69	(66)	7 6	(17)	8 2	3 3	4 3	4 9

Am ... 83 male veterans who survived f... th... fi... nontransmural myocardial infarction and 437 male transmural ... h... survived f... 2 m... th... fi... ... of ... transmural myocardial inf... ... th... group f those ... were ... 40 years ... the gro... f those wh... w... 70 ... were omitted f... m th... table.
†Th... average ... annual mortality rat... ... fifth of th... 5 year mortality rat...
‡Th... rates shown were calculated f... m th... 1943 lif... table f... white males ... the continental United States. The average ... annual probabilit... f dyin... during 5 year period wa... calculated on th... assumption that 1943 ...-specific death rates pr... ...led. These calculated rates w... re th... djusted ... the bas... f th... ... distrib... ... f th... recovered pat... ... in th... study.
§The number ... parentheses is th... number of ... recovered patients ... each age group.

autopsy suggest that the patients described in this report had myocardial infarction One or more of the laboratory evidences of necrosis was found in 74 (79 per cent) of the patients in this study It is very likely that all patients might have shown some evidence of myocardial necrosis if more laboratory examinations had been performed and at optimum times after onset of infarction

Most physicians regard it as particularly important to determine whether myocardial necrosis or only myocardial ischemia is present Myocardial necrosis is generally believed to indicate a more unfavorable immediate and long term prognosis and a need for more vigorous therapy such as prolonged and marked restriction of activity and the use of anticoagulant therapy[2] The absence of associated findings of myocardial necrosis is generally thought to indicate a good prognosis

It is the authors opinion that too much emphasis has been placed on the laboratory findings suggestive of myocardial necrosis There would appear to be no justification for considering the type of patients described in this paper as having had a mild or benign myocardial infarction [8,11] Acute mortality rates of 30 per cent have been reported[12]

The average excess annual mortality rate f recovered patients was 4 to 5 per cent his is not significantly different from the rate found in the transmural groups and appears to be the mortality pattern for all patients with symptomatic coronary artery disease The survival curve[13] for patients with angina pectoris is very similar to the survival curves for patients selected on the basis of having had their first transmural infarction or first nontransmural infarction

Bundle branch block

Twenty three patients were found to have bundle branch block on the first electrocardiogram taken in the hospital and on all subsequent electrocardiograms Of these 10 had left bundle branch block and 13 had right bundle branch block Four patients had only one tracing 4 had two tracings and 15 had three or more electrocardiograms Twelve patients (52 per cent) died within 2 months after onset of their myocardial infarction Six of the 11 survivors died within 5 years

The group is too small for detailed analysis The patients appeared to be older 87 per cent were over 50 years of age as compared to 68 per cent in the nontransmural group and 64 per cent in the transmural group Only 2 patients gave a history of previous hypertension and only 6 patients gave a history of angina pectoris of more than 1 month s duration The pain with onset of infarction tended to be of longer duration than in either of the other groups Nine patients developed shock 8 of these died There was a higher incidence of congestive failure (35 per cent) than in the nontransmural group (10 per cent) or in the transmural group (17 per cent) Significant arrhythmia was observed in 6 patients 4 of whom died during hospitalization

Autopsy findings in cases of persistent bundle branch block

Autopsy protocols were available on 8 patients All of these patients died within 2 months after the onset of their infarctions The infarctions in this group were all large and in every instance seemed to be anatomically transmural although the autopsy protocol frequently was not specific in this regard Marked cardiac enlargement was found in all but one case There were no instances of cardiac rupture or of hemopericardium The coronary arteries were well described in all protocols There was complete occlusion of one major artery in every case and in two hearts both old and new occlusions were described A brief description of each case follows

CASE I H M died on the first day of infarction A huge anterior transmural infarction extended from the apex to the base of the left ventricle The adjacent septum was also involved The heart weighed 375 grams

CASE II E D died 2 days after infarction There was huge infarction which measured 8 by 12 cm in the anterior wall of the left ventricle The heart weighed 460 grams

CASE III J G died on the second day after infarction The anterior infarction extended from the apex t the base and also involved part of the septum The heart weighed 460 grams

CASE IV J C H died on the second day after infarction The infarction was anatomically transmural included the entire circumference of the apex and extended half y to the base anteriorly The heart weighed 600 grams

CASE V S J died on the third day after infarction A posterolateral infarction which included the septum was found The heart weighed 650 grams

CASE VI B S died on the third day after infarction Anterior posterior and septal infarctions were found The heart weighed 420 grams

CASE VII J J H died on the eleventh day after infarction There was a large anterior transmural infarction which included part of the septum The heart weighed 568 grams

CASE VIII H W died on the fifteenth day after infarction The protocol stated that the entire left ventricle and part of the septum was infarcted The heart weighed 510 grams

Discussion

A striking feature of this group of patients is the extremely high immediate and 5 year mortality In view of this high mortality it is thought important to review the prognoses for the patients in the transmural and nontransmural groups who had transient bundle branch block. The patients in the transmural group[1] who showed transient bundle branch block had a 50 per cent immediate mortality and 56 per cent of the survivors died within 5 years Only one patient in the nontransmural group developed transient bundle branch block and he died within 2 months after onset of infarction The poor prognosis of myocardial infarction complicated by bundle branch block has been previously noted [22]

The high mortality rate is not surprising in view of the very large infarctions found at autopsy Rosenbaum and Levine[14] reported that all of their patients who had bundle branch block with an initial myocardial infarction had a past history of hypertension Only one of our autopsied patients (J C H) had a past history of hypertension although cardiac hypertrophy was present in all but one Regardless of the etiology of the cardiac hypertrophy it undoubtedly indicates long standing heart disease This is probably another contributing factor to the poor prognosis for patients who have bundle branch block in association with initial myocardial infarction

The prognosis for patients with bundle branch block has been considered to be that of the underlying disease [?] However in this series and others[1] the prognosis for patients with acute myocardial infarction who develop bundle branch block has been shown to be much worse than the prognosis for similar patients who do not show this conduction defect.

Summary

1 An analysis and follow up is presented of 94 patients with initial myocardial infarction whose electrocardiograms did not show abnormal Q waves The terminology of this variety of ischemic heart disease is discussed and *nontransmural myocardial infarction* is suggested as the most appropriate term

2 The acute and long term prognosis of this group of patients was not significantly different from that of the group with initial transmural myocardial infarction

3 An additional group of 23 patients with initial myocardial infarction whose electrocardiograms showed persistent bundle branch block was analyzed The acute and long term mortality in this group was very high All of the autopsied cases had a large area of infarction and all but one showed significant cardiac hypertrophy

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The infrequent normal electrocardiogram in cardiac pain

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H G Lloyd Thomas M D
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Forty years have passed since an abnormal electrocardiogram was described in cardiac infarction following coronary thrombosis (Pardee 1920) Subsequently a special pattern in the limb lead tracing was identified with the injury when this occupied either an anterior or posterior position in the left ventricle (Parkinson and Bedford) Later the introduction of chest lead electrocardiography made it possible to tell the situation of the infarct with greater precision and a comparison of the electrocardiographic and necropsy findings tested the accuracy of this prediction (Whitten[a] Barnes[1 2] Lyon Myers and associates[H]) Alongside this improved localization of the myocardial infarct a study of certain lesser electrocardiographic signs enabled the recognition of small areas of injury within the myocardium resulting from coronary arterial disease in patients subject to cardiac pain (Evans and associates)

The need of the moment is to render infallible the diagnosis of chest pain and to tell decisively whether it is cardiac pain or not The most painstaking clinical examination cannot accomplish this by itself It is true that a patient whose description of his pain in regard to its site its kind and its response to exercise rest and ingestion of trinitrin conforms to the narrative which custom has decreed as typifying cardiac pain will usually produce an electrocardiogram which endorses its cardiac source Nonetheless the tracing in such a patient often proves to be normal when later and repeated examinations confirm that the pain has its origin elsewhere than in the heart Moreover clinical signs of cardiac pain springing from cardiac infarction are notably sparse in the ambulatory patient so that the story remains objectively unsupported It is in this circumstance that a sure symbol for cardiac pain is an obvious need The question that begs an answer is whether this need is met by the electrocardiogram If this is to be answered in the affirmative three postulates must be satisfied Thus if the electrocardiogram is to stand as the reliable arbiter in deciding the diagnosis between cardiac and noncardiac pain in a patient with an ache in his chest and in whom physical signs like triple heart rhythm are absent it must be established first that exercise does not change a strictly normal resting electrocardiogram into one customarily accepted as abnormal secondly that a normal tracing in one with chest pain does not change within a short period into an abnormal one and thirdly that an electrocardiogram which is abnormal from the effects of coronary arterial disease does not recover wholly with the passage of time

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LEADS | ANTERIOR INFARCTION | LATERAL INFARCTION | POSTERO INFERIOR (LATERAL) INFARCTION | POSTERO INFERIOR (MEDIAL) INFARCTION | SEPTAL INFARCTION

I
II
III
IIIR
CR1,2
CR4
CR7

Fig. 1. The separate designs in salient cardiac infarction in accordance with the site of the injury. In the anterior and lateral varieties significant Q waves may be added.

The purpose of this paper is to describe an investigation in which these postulates were tested in patients in whom chest pain was the presenting symptom.

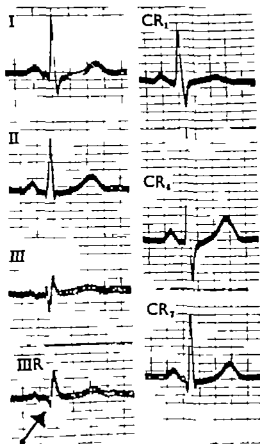


Fig. 2. Limited cardiac infarction. A Q wave absent in Lead III has appeared in Lead IIIR.

We excluded from the study all patients whose cardiac pain arose from either anemia, aortic stenosis, mitral stenosis, or pulmonary hypertension, or was taking place during paroxysms of auricular tachycardia; instances in which the pain arises from causes other than disease of the coronary arteries.

The work has proceeded over a period of 15 years, but naturally not all the patients have been observed that long. During this time an attempt has been made to apply an unequivocal diagnosis in every patient and to trace his subsequent progress.

The *electrocardiograms*, numbering some 7,000, have consisted of the bipolar limb leads I, II, III, and IIIR (Lead III repeated during deep inspiration) and the chest leads CR_1 and sometimes CR_2, CR_4, and CR_7. The unipolar leads aV_R, aV_L, and aV_F were often recorded, but not once did they give information which had not been provided by the standard bipolar leads. The chest V leads were also frequently recorded, but since they proved to be manifestly inferior to CR leads in the portrayal of the significant lesser electrocardiographic changes, they were not subsequently taken routinely.

The electrocardiogram in healthy subjects after exercise

In that an exercise electrocardiogram was habitually recorded in those patients who suffered from chest pain which in every way was *reminiscent of cardiac pain* but

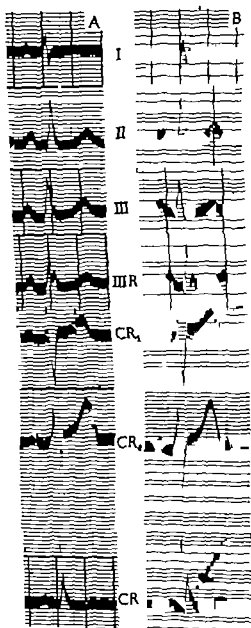


Fig 3 Limited cardiac infarction A flat T w... in Lead I and CR in A has recovered in B where notch in RS is the only deformity in the electrocardiogram

in whom the resting electrocardiogram proved to be a normal tracing it was a prerequisite that the physiologic changes after exercise in a healthy subject should be known and that a statutory pattern accepted as proof of myocardial inadequacy be established Such an investigation was carried out by one of us (Lloyd Thomas [9]) He found that in no healthy subject did strenuous exercise produce changes in the electrocardiogram other than what he regarded as physiologic ones Thus provided the R wave was not tall and exceeding 20 mm a sickle depression meaning a lowering of the early part of the S T segment to 1 mm below the level of the P Q segment did not happen nor did a plane depression a term applied when the S T remains flat for a measured interval of 0 1 second before the tracing rises to form the ascending limb of the T wave nor did the S T descend below the J at any time during its course a previously upright T wave never became flat or inverted the T U segment was never depressed below the level of the P Q segment the U wave was never inverted

Combined clinical and electrocardiographic classification

Patients with chest pain who were examined consecutively through the years were separated into four groups according to the electrocardiographic findings Thus the *first* group comprised those patients with cardiac pain whose electrocardiogram told of salient cardiac infarction Those in the *second* group suffered from cardiac

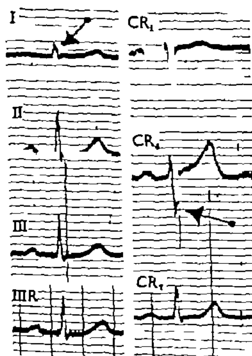


Fig 4 Limited cardiac infarction A notch in the RS segment in Lead I and CR4 the only abnormality ... the tracing

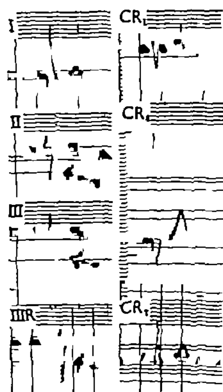


Fig. 5. Limited cardiac infarction. Deep S waves in Leads II, III, and IIIR in the absence of an S wave in Lead I.

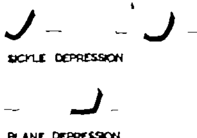


Fig. 6. Schematic representation of significant depression of the S-T segment.

pain and their electrocardiograms provided evidence of a more limited infarct. In a *third* group were patients with cardiac pain whose electrocardiogram proved to be normal at one time and abnormal another time. Patients in the *fourth* group had chest pain historically reminiscent of cardiac pain, but their electrocardiograms remained persistently normal.

This paper is primarily concerned with the last two groups, but emphasis is given to the lesser electrocardiographic signs exhibited by patients who comprised the second group, for a recognition of these has an importance unmatched by any other subject in this field. Only a brief account is given of the first group.

Group I. Cardiac pain: electrocardiogram of salient cardiac infarction. Frank inversion of the T wave in one of more leads, sometimes accompanied by significant Q waves, is the most usual change in the electrocardiogram of patients presenting with cardiac pain. The combination of leads which exhibit such irregularities depends on the location of the infarct, and five electrocardiographic designs have been described as identifying the affected area (Evans [?]) (Fig. 1). Accordingly, infarction of the anterior, lateral, posteroinferior and lateral posteroinferior, and medial and septal areas of the left ventricle are identified respectively by the electrocardiographic designs of T_IT_4, T_IT_1, $T_{III}T_1$, QT_{III}, and Q_I or bundle branch block, where Roman figures are used to designate limb leads and Arabic figures the chest leads. Naturally, on occasion the area traversed by a particular infarct may extend to involve a neighboring sector.

About half of the 2,500 patients with cardiac pain showed one of these designs, and when these were followed up through the years, no electrocardiogram was found *to have recovered wholly, although many*

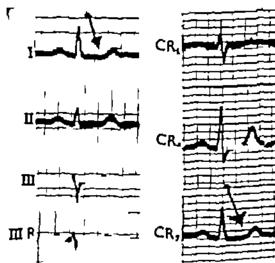


Fig. 7. Limited cardiac infarction. Plane depression of the S-T segment in Leads I and CR from patient who died 4 days later from extension of the infarct.

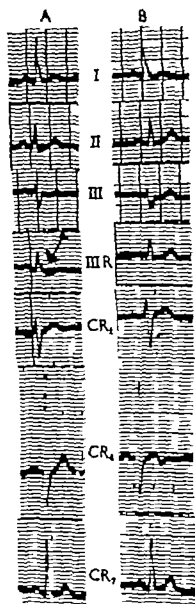


Fig 8 Limited cardiac infarction. Sickle depression in Lead IIIR is the only deformity in *A* recorded 4 years before the extended infarct shown in *B* had taken place

recovered partially leaving behind residual changes usually associated with a more limited infarction a subject to be discussed in the next section

Group II Cardiac pain electrocardiogram of limited cardiac infarction The patients included in this group also form some one half of the 2 500 patients presenting with cardiac pain Each showed electrocardiographic deformities which have been classed as lesser changes (Evans and McRae[8])

and which indicated at the time a more restricted or limited kind of cardiac infarction Although less discernible than those found in salient cardiac infarction the changes have an equal significance as evidence of coronary arterial disease with its unpredictable course Indeed many of the patients exhibiting them showed after the passage of time varying from hours to years the more obvious changes associated with salient infarction In this way their identification with a myocardial injury from the start was confirmed Moreover whenever an exercise electrocardiogram was recorded the existing changes often became exaggerated and other more obvious deformities might be brought to their side Although these specific irregularities are sometimes found in the electrocardiograms of noncomplaining older adults when their significance was being tested it was held conditional that they should not appear in the tracings of healthy young adults

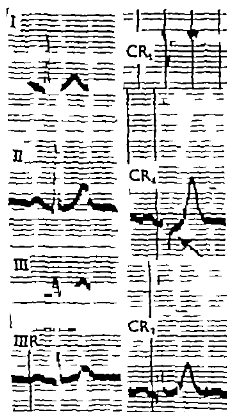


Fig 9 Limited cardiac infarction Sickle depression of the S-T segment in Lead CR_4 the only deformity in the tracing from a patient with cardiac pain

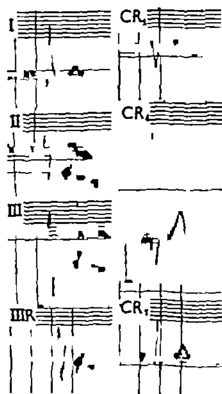


Fig 5 Limited cardiac infarction. Deep S waves in Leads II, III and IIIR in the absence of S wave Lead I

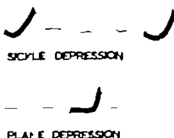


Fig 6 Schematic representation of significant depression of the S-T segment

second group for a recognition of these has an importance unmatched by any other subject in this field. Only a brief account is given of the first group.

Group I. Cardiac pain: electrocardiogram of salient cardiac infarction. Frank inversion of the T wave in one or more leads, sometimes accompanied by significant Q waves, is the most usual change in the electrocardiogram of patients presenting with cardiac pain. The combination of leads which exhibit such irregularities depends on the location of the infarct and five electrocardiographic designs have been described as identifying the affected area (Evans.) (Fig. 1). Accordingly, infarction of the anterior, lateral, posteroinferior and lateral, posteroinferior and medial, and septal areas of the left ventricle are identified respectively by the electrocardiographic designs of T_1T, T_1T_7, $T_{III}T_7$, QT_{III} and Q_1 or bundle branch block, where Roman figures are used to designate limb leads and Arabic figures the chest leads. Naturally, on occasion the area traversed by a particular infarct may extend to involve a neighboring sector.

About half of the 2,500 patients with cardiac pain showed one of these designs and when these were followed up through the years no electrocardiogram was found to have recovered wholly although many had persistent pain and their electrocardiograms provided evidence of a more limited infarct. In a *third* group were patients with cardiac pain whose electrocardiogram proved to be normal at one time and abnormal another time. Patients in the *fourth* group had chest pain historically reminiscent of cardiac pain but their electrocardiograms remained persistently normal.

This paper is primarily concerned with the last two groups, but emphasis is given to the lesser electrocardiographic signs exhibited by patients who comprised the

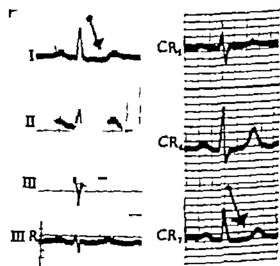


Fig 7 Limited cardiac infarction. Plane depression of the S-T segment in Leads I and CR from patient who died 4 days later from extension of the infarct

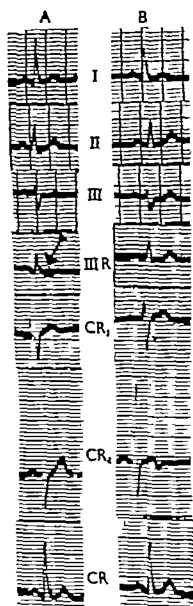


Fig. 8 Limited cardiac infarction Sickle depression in Lead IIIR is the only deformity in A recorded 4 years before the extended infarct shown in *B* had taken place

recovered partially leaving behind residual changes usually associated with a more limited infarction a subject to be discussed in the next section

Group II Cardiac pain electrocardiogram of limited cardiac infarction The patients included in this group also form some one half of the 2 500 patients presenting with cardiac pain Each showed electrocardiographic deformities which have been classed as lesser changes (Evans and McRae[8])

and which indicated at the time a more restricted or limited kind of cardiac infarction Although less discernible than those found in salient cardiac infarction the changes have an equal significance as evidence of coronary arterial disease with its unpredictable course Indeed many of the patients exhibiting them showed after the passage of time varying from hours to years the more obvious changes associated with salient infarction In this way their identification with a myocardial injury from the start was confirmed Moreover whenever an exercise electrocardiogram was recorded the existing changes often became exaggerated and other more obvious deformities might be brought to their side Although these specific irregularities are sometimes found in the electrocardiograms of noncomplaining older adults when their significance was being tested it was held conditional that they should not appear in the tracings of healthy young adults

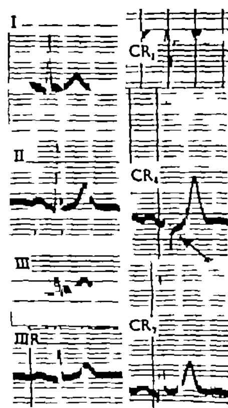


Fig. 9 Limited cardiac infarction Sickle depression of the S-T segment in Lead CR is the only deformity in the tracing from patient with cardiac pain

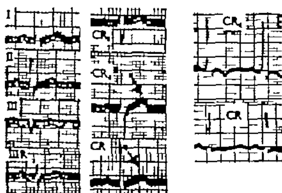


Fig 10 Limited cardiac infarction A low T wave in Leads CR and CR (arrows) became inverted after exercise (E)

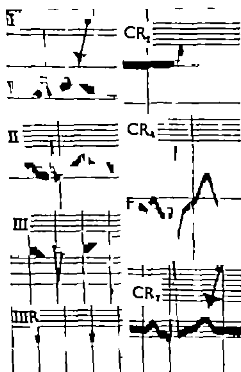


Fig 11 Limited cardiac infarction A blunt T wave in Lead I and CR is the only deformity in the tracing from a patient with cardiac pain who died 2 months later from extension of the infarction.

Experience has confirmed the need to seek these more cryptic signs methodically in seven sectors of the single beat complex they concern the Q wave the RS limb the S wave the S-T segment the T wave the T U segment and the U wave

THE DISTRIBUTION OF NATURAL Q WAVES

Q in IIIR By a natural Q wave we mean one not more than 3 mm in depth nor wider than 0 04 second When a small Q wave absent in the limb lead III appears in IIIR it is unequivocal evidence of a myocardial fault (Fig 2) The sign does not appear in healthy subjects and the lead-combination III and aV_F does not always find it confirming the indispensability of IIIR in the investigation of any patient with chest pain

In extrasystoles Occasionally and in the absence of significant changes in the remainder of the electrocardiogram the appearance of a natural or larger Q wave in a fortuitously recorded ventricular extrasystole in leads other than Lead III has given confirmation of the cardiac source of chest pain

In odd leads The incidence of a natural Q wave in electrocardiograms from healthy subjects and from patients with cardiac pain led Evans and Pillay[9] to conclude that its presence in single leads or in a combination of leads (listed in Table I) provided evidence of a myocardial injury The present study has confirmed this view but it has also emphasized the relative infrequency of the electrocardiographic anomaly as a lone sign of a myocardial fault

THE RS LIMB Notching of the QRS in diverse leads is a common finding in the electrocardiogram of healthy subjects but its presence in CR_7 even by itself is evidence of a myocardial injury (Fig 3) Again its presence in I and CR is similarly a significant but rare sign (Fig 4)

THE S WAVE An S wave greater than the R wave in the limb leads II and III in the absence of an S wave in Lead I has been

Table I Single leads or combination of leads that did not show a Q wave in 500 symptomless and apparently healthy subjects

Number of leads in combination	Leads specified
Single lead	I II IIIR CR_4
Two leads	I and II I and CR II and CR_4 CR_4 and CR
Three leads	I III and IIIR I II and CR_4 II CR_4 and CR III IIIR and CR_4
Four leads	I II III and IIIR I III IIIR and CR_4 I III IIIR and CR II III IIIR and CR_4 III IIIR CR_4 and CR_7
Five leads	I II III IIIR and CR_4 I III IIIR CR_4 and CR

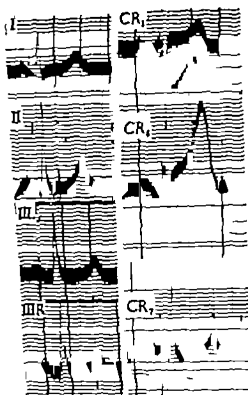


Fig *12* Limited cardiac infarction A sharp descent of *the* T wave in Lead CR (*arrow*) is the only abnormal sign in the electrocardiogram of a patient with cardiac pain A subsequent tracing was grossly abnormal

shown to indicate a lesion in the antero lateral portion of the left ventricle (Wilson and associates[3] Duchosal and Jornod[4] Davies and Evans[5]) In a patient with chest pain this sign may be present alone or in company with other lesser or more obvious signs of cardiac infarction (Fig 5)

THE S T SEGMENT A depression of this portion of the electrocardiogram provides a most important sign of an injured myo cardium unless the effect is due to digitali zation the change affects the segment in its proximal or distal portions producing re spectively either a *sickle* or *plane* de formity (Figs 6 and 7) In one third of the cases in our series the deformity was con fined to IIIR (Fig 8) again emphasizing the importance of this lead in the investiga tion of a patient with chest pain

Another lead in which depression of the S T segment supplies a ready clue to the presence of a myocardial fault is CR Thus in the presence of a moderate S wave a depression of the early part of the S T causing a sickle deformity wherein the J point is lowered below the level of the P Q segment is an abnormality never found in the electrocardiogram of healthy subjects (Fig 9)

THE T WAVE

The low and blunt T A *low T wave* in Leads I and CR or in Leads I and CR_7 cannot by itself be accepted as evidence of a myocardial fault so that in a patient who exhibits this electrocardiographic sign an exercise electrocardiogram has to be recorded in order to decide whether the pain has a cardiac source or not (Fig 10)

On the other hand a *blunt T wave* (Fig 11) in the resting electrocardiogram

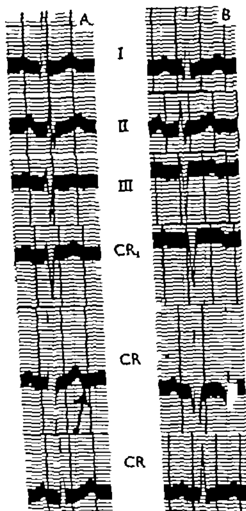


Fig *13* Limited cardiac infarction A terminal dipping in low T wave in Lead CR is the only deformity in *A* recorded a few months prior extension of the infarct shown in *B*

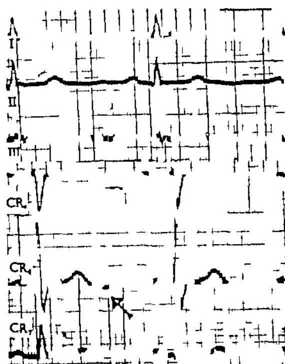


Fig 14 Limited cardiac infarction Depression of the T U segment Lead CR associated with inversion of the U wave in Lead I and II

is pathognomonic of a myocardial lesion even when the wave has hardly lost height

Sharp descent of T in the right pectoral lead This electrocardiographic sign which can by itself identify the cardiac source of pain is uncommon The near vertical drop of the descending limb of the T in Leads CR CR and perhaps CR_3 may be easily appreciated when it is compared with the more gradual decline of the wave in a neighboring lead like CR when simultaneously recorded (Fig 12)

Terminal dip of T wave This is a common finding usually in the apical chest lead in a patient in whom the onset of cardiac pain has been recent a deformity of the T in Lead I commonly accompanies this change It is when it appears as a lone sign and in an otherwise normal electrocardiogram that its recognition assumes importance (Fig 13)

THE T U SEGMENT A casual glance at the electrocardiogram of a patient subject to chest pain may fail to notice depression of the T U as a slight departure of the tracing from the normal because a lowering of this segment by only half a millimeter below the level of a recognizable U P segment confirms the presence of a myocardial lesion So far we have only found this sign in cardiac infarction (Fig 14)

THE U WAVE Inversion of the U wave in a patient with a limited myocardial injury from coronary arterial disease is sometimes it only electrocardiographic sign (Fig 15) The same deformity can also appear as an early change in left ventricular preponderance from any cause and in the absence of an added ischemic myocardial lesion

Group III Cardiac pain one time normal electrocardiogram In only 46 among 2 500 patients with proved cardiac pain was the electrocardiogram a physiologic tracing at one time and an abnormal record at another time This relatively small incidence by itself gives emphasis to the importance of the electrocardiogram in deciding whether a patient with chest pain has cardiac pain Yet it is large enough to invalidate the test as one which could invariably provide an infallible answer unless it can be shown

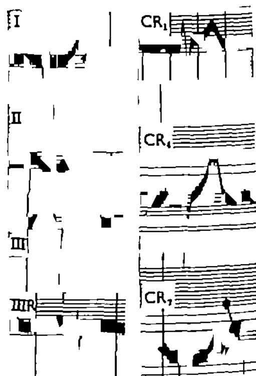


Fig 15 Limited cardiac infarction Inversion of the U wave in Lead CR is the only deformity in the tracing from patient with proved cardiac pain Inversion of the T in Lead III is corrected in Lead IIIR

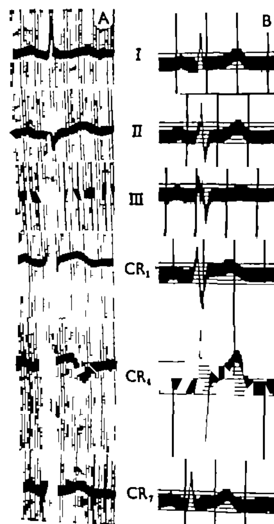


Fig 16 The mutable electrocardiogram (Type I) A low T wave in Lead I inverted T in Lead CR and terminal dipping of the T in Lead CR seen in *A* are absent in *B* recorded some time later

that these 46 patients presented a peculiar type of tracing which labeled them as distinctive and as exhibiting pain which is prognostically less sinister than the one arising from frank cardiac infarction The changing electrocardiograms recorded in patients forming this group therefore came under special scrutiny and they were found to conform to two types

THE MUTABLE ELECTROCARDIOGRAM (TYPE I) In 33 of the 46 patients the tracing assumed the pattern described by Evans in which the T wave was low and usually inverted in the limb lead I and in chest leads reaching from the right pectoral (CR_1) as far as the apical lead (CR_4) and usually beyond (Fig 16) These changes were distinctive in regard to the specific leads which showed the T wave deformity and were not accompanied by significant Q waves nor by depression of the S T segment If by chance either of these two faults were added although recovery of the deformed T waves might have taken place residual changes in some part of the tracing remained as evidence of cardiac infarction limited though it was to a small area (Fig 17)

Evans postulated that this mutable electrocardiogram indicated a diffuse and intense cardiac ischemia from interruption of the blood flow in the left coronary artery The wide distribution of the T wave inversion suggested that the artery was involved

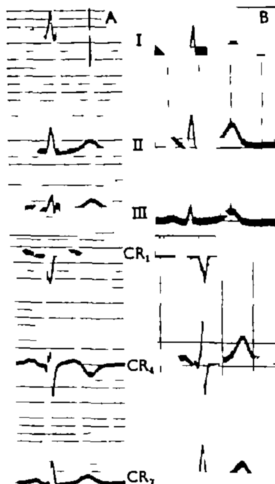


Fig 17 Limited cardiac infarction The tracing *A* simulates *A* in Fig 16 except for the presence of Q wave in Lead CR and this abnormality persists in the largely recovered tracing in *B*

ne its source Such interruption is short lived and does not last long enough to cause more than a transient heart muscle cell dysfunction Within 3 to 6 months and sometimes sooner the myocardium regains it electrically normal state when attacks of cardiac pain cease to recur It is likely that the episode is caused by spasm of the artery unaffected by material atherosclerosis and it is because of its innocent nature that its recognition is so desirable in the occasional subject presenting it

THE MUTABLE ELECTROCARDIOGRAM (TYPE II) In the other 13 patients in whom an electrocardiogram which was abnormal at one time was normal at another time the tracing again assumed a uniform pattern but different from the previous kind In this instance when the tracing was abnormal the T wave was inverted in Leads III and IIIR and low or sometimes inverted in Lead II whereas a significant Q wave was absent from these leads and the T was normal in CR_7 (Figs 18 and 19) In this last respect therefore and in its characteristic behavior of reverting to a normal tracing it differed from the electrocardiogram standing for salient cardiac infarction of the posteroinferior and lateral portions of the left ventricle wherein the T is inverted in CR as well as in the limb leads

Although arteriospasm of the kind described for the previous type of mutable electrocardiogram may be operating to produce this tracing it could have another explanation Thus an interruption of a branch of the right coronary artery may have taken place in the presence of an efficient collateral circulation which ensured the survival of those heart muscle fibers subjected to the transient ischemia (Lowe[11] Blumgart and associates[6])

Group II Cardiac like pain persistently normal electrocardiogram Among 3 546 patients with chest pain which was in every way typical of cardiac pain in regard to its site it kind and its relation to rest or exercise and even sometimes in respect to its relief by trinitrin the resting electrocardiogram proved to be a normal tracing in some one third of them Moreover it remained normal when recorded at subsequent examinations after periods of months or even years and an exercise electrocardiogram never showed changes indicative of the effects of coronary arterial inadequacy

In the majority of the patients functional dyspepsia was considered to be the cause of the pain so that many gave a history of habitual constipation and excessive flatulence and showed esophageal arrhythmia during a barium swallow and a cup and spill design of the opaque meal when it entered the stomach which was bent on itself by much gas in the splenic colon

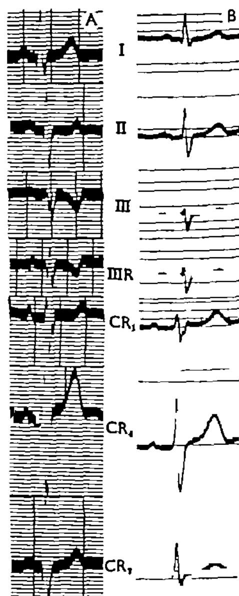


Fig 18 The mutable electrocardiogram (Type II) In *A* the T wa is low in Lead II and deeply inverted in Lead III and IIIR These changes are absent in the normal tracing (*B*) recorded later when the patient was no longer liable to cardiac pain

Table II The extent to which the electrocardiographic deformity was exaggerated after exercise in 20 patients who showed lesser electrocardiographic signs with cardiac pain and in 20 patients with similar electrocardiographic changes but without pain

Pain	Number of patients	Extension of pain in electrocardiographic changes after exercise			
		Absent	Slight	Moderate	Prominent
Present	20	0	4	4	12
Absent	20	2	13	5	0

Many lost their symptoms when anti dyspeptic measures were introduced or when reassured that nothing ailed the heart and in none was it necessary at subsequent examinations to retract such reassurance once it had been given on the basis of finding a strictly normal electrocardiogram during a time at which the patient was liable to periodic attacks of pain

The place of the exercise electrocardiogram in the diagnosis of cardiac pain

In the past the exercise electrocardiogram has proved useful to test the significance of certain small signs in the tracings of patients with cardiac pain recorded at rest Now that these have become known the test need only be applied for diagnostic purposes in the case of one of them namely when the T wave is low in Lead I and in Leads CR_4 or CR_7 for this change can be present in circumstances other than cardiac pain and not infrequently in health

It is known (Biorck[4] Master[19]) that the exercise test in patients who have contracted cardiac infarction may show fewer abnormalities with the passage of time presumably this reflects the development of a more adequate collateral circulation and so the exercise electrocardiogram may prove useful in estimating the efficiency of this alternate blood supply In order to test the validity of this assumption we compared the extent of the electrocardiographic changes which followed exercise in 20 consecutive patients who showed limited cardiac infarction and cardiac pain with those in 20 patients who had no chest pain but in whom a routine electrocardiogram showed changes of limited cardiac infarction like unto the former group (Table II)

In the first group with cardiac pain an increase in the changes was prominent in 12 moderate in 4 and slight in only 4 (Fig 20) In the second group without chest pain exaggeration of the changes was never prom

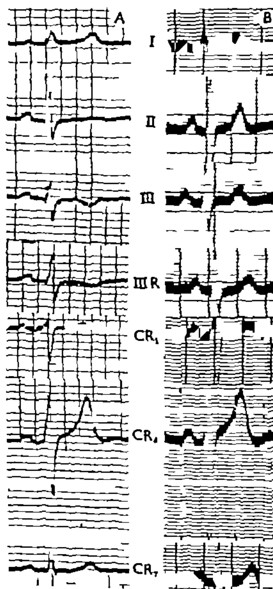


Fig 19 The mutable electrocardiogram (Type II) I of the T wave is flat in Lead II and inverted in Lead III and IIIR. These changes are absent in the normal tracing (B) recorded later when the patient was no longer liable to cardiac pain

ment it was moderate in only 5 cases li ht in 13 and absent in 2 cases (Fig 21) Thus the exercise electrocardiogram has greatest value in the examination of adults when an obligatory examination has included an electrocardiogram which has uncovered the characteristic signs of limited cardiac infarction and when the subject in order to win some advantage might be suppressing a history of chest pain This circumstance might arise in the course of an examination for life insurance or when the examination which has to include electrocardiography is conditional for an election into a superannuation scheme It would seem to be fair inference that if the changes in the exercise electrocardiogram are conspicuous pain on effort is to be expected in most ca es on account of the proved inadequacy of the collateral circulation Conversely if such changes are inconspicuous pain may be absent because of an efficient alternative blood supply

A positive exercise test in the rare cases exhibiting the mutable electrocardiogram is only obtained during a period which immediately follows the return of the tracing to normal and it is not expected at a later period when the patient is remaining free from chest pain

In the fourth group of cases in which the *resting electrocardiogram is a strictly normal* tracing during a time when recurrin paroxysms of chest pain are strongly presumptive of cardiac pain the exercise electrocardiogram will not show signs indicative of inadequacy of the coronary circulation

Summary and conclusions

Pain in the chest is a common complaint Its description in terms of character place and spread and its reaction to exercise or to rest cannot predict its source with certainty Moreover the sparsity of physical signs in a patient with cardiac pain is notable so that undue reliance on the history frequently misleads in diagnosis A search therefore has been directed to finding a formula which can tell unequivocally whether a pain in the chest arises from the heart or not It is known that certain abnormalities in the electrocardiogram of one with chest pain have their source in cardiac infarction but the ability of a normal tracing to exclude cardiac pain has not yet received universal acceptance

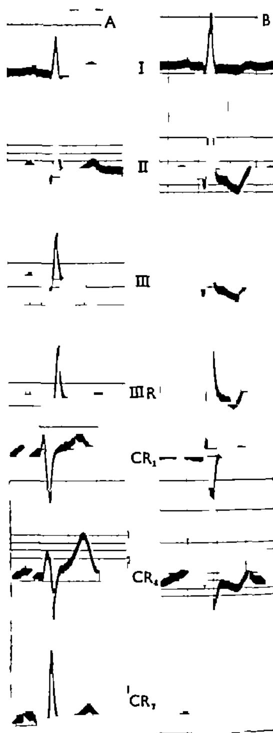


Fig 20 The effect of exercise on the electrocardiogram in limited cardiac infarction with chest pain S-T depression in Leads III and IIIR in the resting electrocardiogram (*A*) After exercise (*B*) there is gross S-T depression in several lead

The clinical and electrocardiographic supervision over a period of 5 to 15 years of 3 546 patients with chest pain which was presumed from the history to be cardiac pain found that they fell into four groups

Some one third of the patients belonged to the *Group I* in which the design of the electrocardiogram confirmed the presence of *salient cardiac infarction* According to the place of the infarct the T wave was inverted in either Leads I or CR_4 or in both (anterior distribution) in Lead I and CR (lateral) in Leads III and CR (*posteroinferior* and *medial*) *In septal* infarction the Q was deep in Lead CR_1 and in leads more to the left or a bundle branch block was present A significant Q wave was *often present in the first two designs* and in the last four the S T segment was depressed in Lead IIIR Naturally two or more of the designs appeared together when the infarct trespassed on adjoining areas

Another third of the patients belonged to the *Group II* in which cardiac pain was associated with lesser electrocardiographic changes which told of a more *limited cardiac infarction* at the time Such changes included a natural Q in Lead IIIR when it was absent in Lead III a notch in RS a deep S wave in Leads II and III when S was absent in Lead I depression of the early (sickle) or late (plane) portions of the S T segment in any lead particularly Lead IIIR with the exception of Lead III a low T in Leads I and CR_4 or CR blunt T wave sharp descent of the descending limb of the T wave in the right pectoral lead terminal dipping of the T wave especially in Lead CR_4 depression of the T U segment and inversion of the U wave

Many electrocardiograms in the first group moved *in time to resemble those in* the second group and similarly from the second to the first

Group III comprised only 46 patients with cardiac pain resulting from *temporary ischemia* in whom the electrocardiogram was abnormal at one time and normal at another time The mutable electrocardiogram in these cases conformed with one of two designs In the first of which there were 33 examples the T wave was either low or inverted in limb lead I and was inverted in chest leads CR_1 to CR_4 and even beyond The tracing which showed neither significant Q waves nor depression of the S T segment recovered completely in time usually in the course of 3 months In the second variety of mutable elec

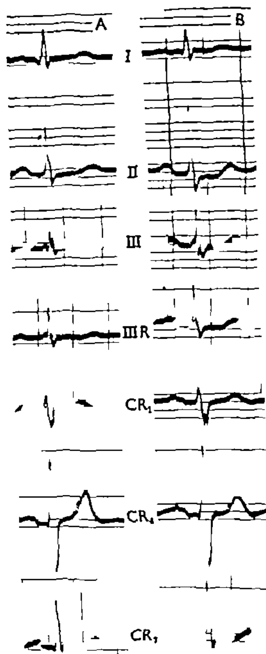


Fig 21 The effect of exercise on the electrocardiogram in painless limited cardiac infarction Depression of the S-T segment in Lead II III IIIR and CR_7 in the resting electrocardiogram (*A*) are only slightly exaggerated in *B* recorded after exercise

trocardiogram of which there were 13 examples the T wave became inverted in Leads III and IIIR and low in Lead II again in the absence of both significant Q waves and S T depression and also without lowering of the T wave in Lead CR this last finding differentiates it from posteroinferior cardiac infarction Three of our patients in whom a mutable electrocardiogram of the first design had recovered developed later the electrocardiogram of the second design and then again recovered completely

Yet another one third of the patients with chest pain belonged to *Group IV* in which the electrocardiogram was a normal tracing which remained so during a period of observation lasting many years In the majority of these examples of *cardiac like pain* a barium swallow and the response of the patients to appropriate therapy confirmed a functional dyspepsia as the cause of the pain

The recognition of the truth that a strictly normal electrocardiogram excludes cardiac pain if recorded during a period when a patient is liable to paroxysms of chest pain even should the description of his symptom presume a coronary arterial source ensures for innumerable subjects a protection against a life of unwarranted invalidism

It is suggested that the exercise electrocardiogram can play a part in assessing the significance of the lesser electrocardiographic signs identified with coronary arterial disease when they are found during an obligatory medical examination such as the one connected with an application for life insurance and when chest pain is either absent or when a history of it is deliberately withheld

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Experimental and laboratory reports

Movement of the heart during the period between the onset of ventricular excitation and the start of left ventricular ejection

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The present communication is the first of several aimed at a more precise definition of the mechanical sequence of the heart beat. This definition is based on the close agreement between the results of the application of two unrelated indirect techniques to two different species under widely varying experimental conditions. The methods utilized have been extended and improved since the preliminary report of this work.

During the isometric phase of systole there is a continuing increase in the number of fibers which have entered into contraction. Thus one might expect to observe not only a steady rise in the actual pressure but also a progressive increase in the rate of rise in pressure. However, the latter condition is not fulfilled. Despite the increment in the actual pressure, the *velocity of rise is irregular and jerky* in both ventricles (Fig. 1). This has been true not only in all dogs but in numerous human subjects who have been studied at operation or by cardiac catheterization. We think it improbable that these irregularities in the rate of rise in pressure are due to artifacts because they tend to be constant not only from cycle to cycle but from subject to subject. Furthermore, the directional changes in the velocity curves are often reflected as changes in slope in the conventional pressure records. Indeed, the chief advantage of the former traces is their great detail, in that they show more frequent alterations in direction and may exhibit changes in slope which cannot be detected in the undifferentiated pressures.

The simultaneous study of pressure velocity curves from two adjacent cardiac chambers appears to offer an explanation for this apparent paradox, i.e., the observation that despite the steady increase in the number of contracting fibers the rate of rise in pressure is not smooth but irregular. Thus, as is shown in Fig. 1, there is at times a reciprocal relationship between the velocity curves from the two ventricles; a decreasing rate of rise in one chamber is associated with an increasing rate in the other. This phenomenon, which has been regularly observed, is probably due to motion of the interventricular septum toward one ventricle and away from the other.

Similar reciprocal changes in the pressure velocity curves have been consistently found in the records from the aorta and from the

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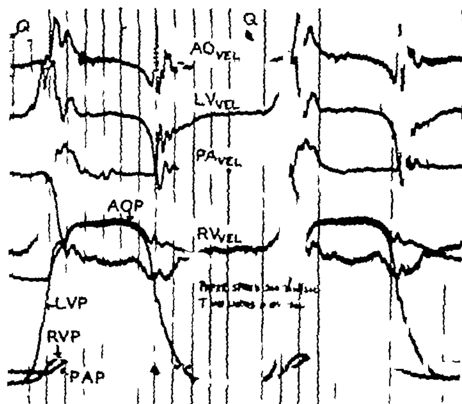


Fig. 1. The pressure traces from the two ventricles (*LVP*, *RVP*), the aorta (*AOP*), and the pulmonary artery (*PAP*) of a dog are shown. The first time derivative (dP/dt) of these pressure pulses is also illustrated (*LV*, *RV*, *AO*, *PA*). The velocity traces display much more detail than the undifferentiated pressure records from the same chambers.

left ventricle and are thought to be caused by movement of the semilunar valves either toward the aorta (ballooning because of the higher pressure below) or toward the ventricle (pull on the aortic ring). Reciprocal changes also occur between the right ventricle and the pulmonary artery and between each atrium and the corresponding ventricle. These findings have provided an indirect method of studying the movements of the structures (valves, interventricular septum) which separate the cardiac chambers from each other and from the great vessels. The correlation of such movements with the precordial motions in order to gain an insight into the genesis of the latter is the main objective of this and subsequent reports.

Subjects and methods

Kinetocardiograms were recorded from 41 healthy adults. In 22 of these persons traces were obtained only from the four areas corresponding to the V_1 to V_4 electrocardiographic points. Nine subjects had similar traces plus records of the heart sounds from the mitral, tricuspid, pulmonic, and aortic areas. The last 10 individuals were deliberately selected from young (19 to 26 years, 3 males and 2 females) and middle-aged (46 to 59 years, 4 males and 1 female) groups. They were studied in more detail: precordial tracings were obtained from the second to the sixth intercostal spaces inclusive in vertical lines corresponding to the V_1, V_2, V_4, and V_6 lines. Movements in the V_3 line were not recorded because they are usually similar to those from the V_2 and V_4 areas. Likewise for these 10 subjects records were obtained from the suprasternal notch and from the right and left epigastric regions.

When the records from these 41 subjects were analyzed, it soon became apparent that those from the 10 persons who were subjected to the chest mapping procedure contained more pertinent informa-

tion than could be found in the traces from the other 31 individuals who were studied less intensively. Consequently the several tabulations presented in this and succeeding reports deal only with the data from these 10 persons. However the findings in this group are also representative of those in the larger number of subjects.

In 18 open chest dogs pressures were recorded from the aorta pulmonary artery and from the four cardiac chambers. The curves representing the change in velocity of pressure were obtained by electronic differentiation of the pressure pulses. The recording system consisted of metal cannulae connected to strain gauge transducers (Statham P23Db) of equal sensitivity and an 8 channel oscilloscopic recorder (Electronics for Medicine). The frequency response of the system was tested by a sine wave pressure generator and appeared to be flat to more than 100 cycles per second. The cannulae were introduced into the cardiac chambers through the respective atrial appendages and into the roots of the great vessels through appropriate branches. The position of all cannulae were verified at autopsy.

Because of experimental difficulties simultaneous tracings from all adjacent areas were not always secured. In the analysis of the data only technically satisfactory records were studied.

Explanation of terms. The kinetocardiographic (KCG) areas are designated as in previous publications. The first subscript to letter K refers to the vertical V lines as used in electrocardiographic terminology whereas the second subscript indicates the intercostal space. Thus K_{13}, K_{45} and K_{54} refer respectively to records obtained from the right parasternal line in the third intercostal space, from the mid clavicular line in the fifth intercostal space and from the anterior axillary line in the fourth intercostal space. Traces from the suprasternal notch and the right epigastric and left epigastric regions are indicated by K, K and K respectively.

The designation of the specific events of the cardiac cycle poses a more complex problem. One desideratum is that the motions be labeled in their normal sequence and according to some generally accepted subdivision of the cardiac cycle. Even though both dogs and men display a common general sequence this is not absolute and varies in detail from one individual to another within the same species. Likewise there are relatively few subdivisions in Wigger's classic separation of the cardiac cycle whereas the cardiac motions are much more numerous.

An ideal description of the cardiac movements would include both anatomic and physiologic components. One would like to know not only the precise structure responsible for but also the exact mechanism whereby it produces the motion in question. Although the studies seem to supply certain suggestive evidence related to these questions there are several exceptions.

These considerations have led to the adoption of the following procedure in designating the movements. The major phases of the cycle of ventricular activity are indicated by the letters C (contractile movements observed between the onset of excitation and the start of left ventricular ejection) J (ejection) and R (relaxation). These letters are preferred to I (isometric) and E (ejection) in order to avoid confusion with the terms used in an earlier publication[1] from this laboratory which was of a descriptive nature and was presented prior to recent information concerning the possible mechanism of the motions.

Between the times of excitation and of left ventricular ejection 10 different precordial deflections are commonly seen. Therefore for the purpose of simplicity this period is subdivided into CI (start of excitation to beginning of first heart sound) CII (onset of first sound to beginning of right ventricular ejection) and CIII (right ventricular to left ventricular ejection). An attempt has been made to designate by one or more letters and within parentheses the specific structure which is believed to be particularly related to the movement in question. Finally in order to emphasize the distinction of the small motions from the larger ones a capital letter is used in referring to the latter. The term *CI(pl)* then means that during isometric contraction before the start of the first sound a small motion is observed that is believed

[illegible]

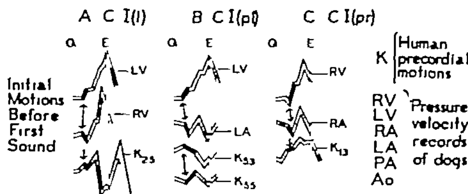


Fig. (For legend see opposite page)

to be due to the contraction of the papillary muscles of the left ventricle. Likewise the expression $CII(S)$ indicates that contraction of the septum is thought to be responsible for a large motion occurring after the onset of the first sound but before the start of right ventricular ejection.

This system of nomenclature, although cumbersome, appears to be less confusing than the others which we have attempted.

Results

For the sake of clarity the several motions of both species are integrated in Fig. 2. This is a diagram and displays those movements which were either invariably or frequently observed. The actual data from the human subjects are summarized in Table I and illustrated in Figs. 3-5, and those from the dogs are shown in Table II and Figs. 4, 6, and 8.

Terminal atrial movements at the onset of ventricular excitation. All subjects exhibited an outward motion starting just before or after Q in two or more of the right parasternal traces (Fig. 3, C and D).

At the other precordial regions this upstroke was less frequently seen. These motions were small.

The atrial pressure velocity traces of the dogs commonly exhibited a slight decline usually starting shortly before the beginning of ventricular excitation (Fig. 4).

COMMENT. In previous reports[3] evidence indicating that these motions are of atrial rather than ventricular origin was presented. Thus similar precordial movements are encountered after isolated P waves in patients with heart block and are absent in subjects with auricular fibrillation. Presumably these deflections are related to relaxation of the left atrium. Filling of the atria as they relax is probably also concerned (Fig. 4).

Aside from the terminal atrial forces a regular sequence of deflections due to ventricular activity was noted.

I. Initial ventricular motions starting before the first heart sound. At about 0.035 second after Q three precordial motions were seen (Fig. 2, A, B, and C). All subjects exhibited outward or inward deflections in the K and K_4 lines (Fig. 5). Most of them displayed inward motion in the right parasternal region (Fig. 3, C and D) and some showed reciprocal movement (inward above, outward below) in the left anterior axillary line (Fig. 3, A and B, Table I).

The conventional pressure records and the pressure velocity traces from the left ventricle of the dogs usually began to rise about 0.01 second before those from the right. In most of the animals the right ventricular velocity record showed a slight downward dip either before or just after its initial rise (Figs. 4 and 6).

It should be realized that the designation of a given structure as being responsible for an observed motion is at present hypothetical and must be considered as tentative pending confirmation secured by more direct means. For this reason the abbreviations which indicate structures are placed in parentheses. The division of the early portion of the cardiac cycle into three parts is an oversimplification. Actually there is first a phase of electromechanical lag and then the three phases mentioned above. It should also be noted that the term isometric contraction as commonly used to indicate the period between the onset of the first heart sound and the start of ejection is different for the two ventricles because the right chamber ejects first in the normal human subject. Furthermore the precordial tracings exhibit ventricular motions which start 0.01 to 0.02 second before the first heart sound, and a similar phenomenon is seen in the pressure velocity traces of the dogs.

The atrial velocity traces commonly exhibited decline as the ventricular pressures rose (Fig 4 Table II) This dip was sometimes preceded by an initial rise These atrial motions were seen in an animal with heart block during ventricular complexes which were removed from P waves They therefore are due to initial ventricular rather than to terminal atrial activity

COMMENT The findings illustrated in Fig 4 indicate that at the onset of isometric contraction the interventricular septum of the dog tends to move to the left (pull

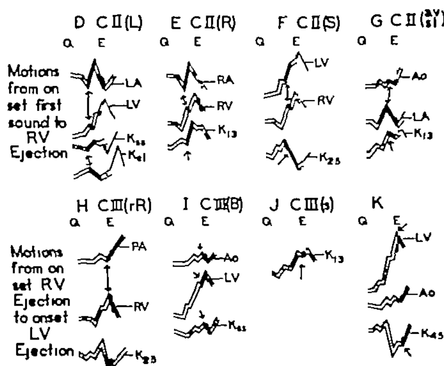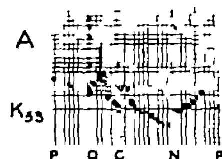
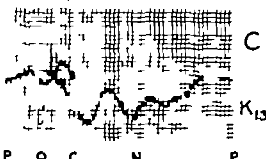
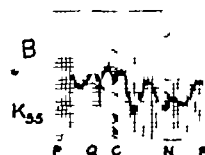


Fig 2 This diagram illustrates all of the motions occurring between the onset of excitation (*Q*) and the start of left ventricular ejection (*E*) The velocity traces (vel) of the dogs and the precordial movements (*K*) of the human subjects are adjusted to a time scale corresponding to an identical duration of isometric contraction in the two species The specific motions are designated by the arrows and by the black areas *A* The downstroke in the precordial (K_{45}) and the right ventricular records as the left ventricular trace starts to rise are ascribed to a backward leftward pull on the interventricular septum *B* The downstrokes in the left atrial and upper left axillary (K_{41}) records associated with upstrokes in the left ventricular and lower axillary trace are attributed to contraction of the left papillary muscles *C* Similar reciprocal changes in the right chambers and the small inward motion in the right parasternal (*K*) region probably represent right papillary contraction *D* The abrupt rise in the left atrial record is ascribed to mitral closure At the same time the inward movement in the epigastrium (*K*) and the outward deflection in the suprasternal area (*K*) point toward headward displacement of blood *E* Rightward motion of blood and tricuspid closure appear to be responsible for the upward deflections in the right parasternal area (K_{13}) and in the right atrial record *F* The large backward motion of the precordium (K_{25}) is accompanied by respective increase and decrease in the rate of rise in pressure in the left and right ventricles These phenomena can be explained by contraction and leftward movement of the interventricular septum *G* Downstrokes in the atrial aortic and right parasternal records are ascribed to motion of the atrioventricular and possibly the semilunar ring toward the apex *H* The abrupt decrease in the velocity of rise in pressure in the right ventricle associated with the large upstroke in the pulmonary artery trace indicate right ventricular ejection which is accompanied by a small forward (recoil) movement in the precordial (*K*) trace *I* The downstroke in the aortic and suprasternal (*K*) records associated with steeper rise in pressure in the left ventricle point toward downward pull on the aortic ring *J* The small outward motion in the right parasternal area is not regularly associated with analogous changes in the records from the dogs It is uncertain whether this movement is related to rightward displacement of the interventricular septum or to bulge of the tricuspid valve into the right atrium *K* The end of the left ventricular isometric period is indicated by the abrupt upstroke in the aortic trace and the simultaneous decrease in the rate of rise in pressure in the left ventricle At the same time the apical (*K*) trace shows a second and larger outward recoil The motion [I(rL)] is not labeled as such in the figure because it occurs during ejection rather than during contraction







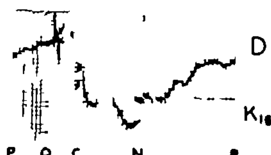


Fig. 3. Some of the motions during isometric contraction. Paper speed 50 mm. per second. All tracés start and end at onset of the P wave. Vertical lines indicate onset of excitation (*Q*), of carotid upstroke (*C*), and of carotid incisural notch (*N*). *A* and *B*. At 0.04 sec. after Q a small inward motion is seen in the third intercostal space in the left anterior axillary line (K_{35}) at the same time at which outward movement begins in the fifth intercostal space (K_{55}). These deflections which are more pronounced in this subject than in most others are ascribed to contraction of the papillary muscles of the left ventricle. They are designated in the text as CI (pl). At 0.07 to 0.08 sec. after *Q* both records exhibit downstrokes. These are possibly related to descent of the mitral annulus [CII(*)] with decrease in the transverse diameter. *C* and *D*. Small upstrokes attributed to atrial relaxation occur as ventricular excitation starts. About 0.04 sec. later a minimal inward motion (*arrow, first one above*) is seen. This is believed to be related to contraction of the right papillary muscles and is called CI(pr) in the text. The next motion (*second arrow*) occurs about 0.0 sec. later, is outward, and is designated as CII(R). In this subject, as in most others, it is larger in the upper (*C*) than in the lower (*D*) right parasternal intercostal spaces. It appears to be closely associated with tricuspid closure (see text). Both traces exhibit very small inward then outward deflections after the second arrow and before the large downstroke which signifies the change in volume due to ejection. The small inward movement is designated CII(*) and is attributed to downward pull on the tricuspid annulus. The subsequent tiny upstroke is called CII( ) and is ascribed to rightward displacement of the interventricular septum.

by left ventricle). A similar explanation probably accounts for the inward motion sometimes seen in the left precordial (K_3 and K_4) records. Since the left ventricle which usually starts to contract first* appears to be mainly responsible for this small initial motion, it is designated as CI(l).

*The initial outward motion which was often seen in these areas may be related to rightward displacement of the septum by the rising pressure in the left chamber.

The observation of reciprocal motion with downstrokes in the upper and upstrokes in the lower intercostal spaces in the left anterior axillary traces of some of the human subjects (Table I) accords well with the usual finding in the dogs (Table II). In the animals the left atrial velocity curves exhibited a decline soon after the left ventricular pressure began to rise. The similar phenomena observed in the right chambers of the dog appear to

correspond to the small inward motion of the human right parasternal region. These several findings point toward descent of the atrioventricular cusps. Conceivably such motions might be due to a downward pull on the rings of these valves. However it is more likely that contraction of the papillary muscles which are excited early is the mechanism responsible. These two movements are therefore tentatively designated as CI(pl) and CI(pr).

II. Movements occurring between the first heart sound and the onset of right ventricular ejection

CII(L) HEADWARD MOTIONS AT THE TIME OF MITRAL CLOSURE. Three different observations in the human subjects suggested that blood was being displaced headward during the early phase of ventricular contraction, i.e., 0.04 to 0.07 second after the QRS onset. (a) Four individuals exhibited a downstroke in the epigastric traces (Figs. *2 D* and *7 A*), meaning either headward or backward motion of the inferior surface of the heart; at the same time each of them had an outward motion in the second and third intercostal spaces at the K_2 or K_4 areas. (b) Five persons displayed an upstroke in the upper left precordial region associated with the downstroke in the lower (fifth and sixth intercostal spaces) areas. (c) Six subjects exhibited a small upstroke in the trace recorded from the suprasternal notch (Figs. *2 D* and *7 B*). Nine of 10 persons exhibited one or more of these headward motions. The time of onset of

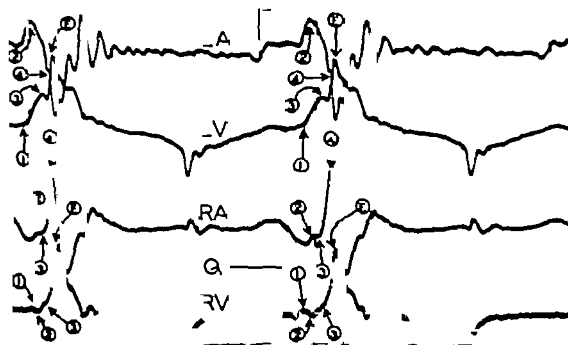


Fig. 4. The pressure velocity curves of the four cardiac chambers of a dog are shown during two successive cycles starting and ending at Q. Time lines are 0.04 sec. part A: ventricular excitation starts; the atrial curves are declining (relaxation). The subsequent rise 0.02 sec. later is presumably due to atrial filling. *1*. At 0.03 sec. after Q the left ventricular trace (*LV*) begins to increase whereas there is slight decline in the right ventricular record (*RV*). This is attributed to a leftward pull on the septum. *2*. About 0.04 sec. after the start of excitation the right ventricular pressure starts to rise and the atrial traces exhibit either a decline (*LA*) or an abrupt leveling of the previous upstroke (*RA*). These changes are ascribed to contraction of the papillary muscles with downward motion of the atrioventricular cusps. *3*. As the right ventricular curve becomes steeper there is a sharp upstroke in the right atrial trace and at the same time the rate of rise in pressure in the left ventricle decreases. It would appear that the interventricular septum is being displaced to the right as ascent of the tricuspid leaflets occurs. The mitral closure upstroke in the left atrial trace was smaller (notch in the downstroke between second and fourth arrows) in this dog than in most. Ascent of the tricuspid leaflets occurred unusually early in this animal. *4*. The sharp decline in the rate of rise in ventricular pressure denoting ejection (*E*) occurred 0.07 sec. after Q. About 0.01 sec. before this both atrial traces displayed a sharp downstroke which is attributed to descent of the atrioventricular rings toward the apex.

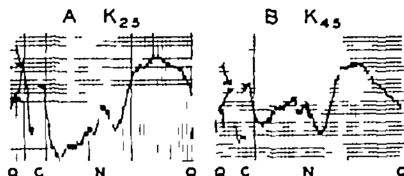


Fig. 3. Motions of the left lower precordial region during isometric contraction. Paper speed 50 mm. per second. Traces start and end with ventricular excitation, illustrating one complete cycle. *C* and *N* refer respectively to start of carotid upstroke and to incisural notch. The outward motion as excitation starts is attributed to atrial relaxation. The second portion of this biphasic upstroke (*first arrow*) is probably related to change in shape of the right ventricle, and is due either to contraction of the papillary muscles or to displacement of the septum as the left ventricular pressure starts to rise [CI(1)]. The second arrow indicates the large inward motion of the fifth intercostal space in the left parasternal (*A*) and mid-clavicular (*B*) lines. This is ascribed to contraction and backward movement of the interventricular septum [CII(S)]. After the downstroke a large outward deflection is observed. The biphasic nature of this movement is clearly seen in *A*. The small initial component begins 0.09 sec. after Q and 0.04 sec. before the carotid upstroke. This movement is thought to represent right ventricular recoil and is designated CIII(R). The larger component which starts 0.02 sec. later and is also present in *B* is ascribed to left ventricular recoil.

these deflections corresponded with the beginning of the mitral first sound (0.053 ± 0.013 second) in 8 of 9 subjects.

At this time of the cycle or about 0.01 second later, traces of pressure velocity from the pulmonary artery and from the aorta of dogs sometimes displayed a small rise (Fig. 6). All of the atrial traces showed either an upstroke or a notch in the downstroke previously mentioned (Table II, Figs. 4 and 8). The close relationship of this left atrial upstroke to the mitral first sound is indicated in Fig. 8.

Comment. These data point toward headward motion of the blood. In the case of the dogs the upstroke in the left atrial trace indicates mitral closure. The slight rise occasionally seen in the pressure velocity traces from the aorta and from the pulmonary artery signify bulge of the semilunar valves into the great vessels. The findings in the human subjects likewise point toward headward movement of blood as mitral closure occurs.

CII(R). RIGHTWARD MOTION AT THE TIME OF TRICUSPID CLOSURE. An upstroke was present in the right parasternal areas in each subject (Fig. 2 *E*). This outward deflection usually started 0.05 to 0.06 second after Q. The extreme limits were 0.03 and 0.075 second. The size varied from a flattening of the preceding downstroke (amplitude 0) to 5 mm. The absolute size was slightly greater and the relative amplitude much larger in the higher than in the lower intercostal spaces (Fig. 3 *C* and *D*), being somewhat larger in the second than in the others (Table III).

Comparisons were made in 9 normal subjects of the time of onset of this right parasternal outward movement and of the tricuspid component of the first heart sound. The latter phenomenon occurred within the range of 0.01 ± 0.01 second after the former.

Right atrial pressure velocity traces from the dogs showed a rise at about 0.05 second after the start of the QRS (Table II, Fig. 4). This motion corresponded in time to the tricuspid component of the first heart sound (Fig. 8).

Comment. These data suggest that the right parasternal outward motion which occurs about 0.055 second after Q is prob-

ably related to rightward displacement of blood as tricuspid closure occurs. The finding that this deflection is larger in the upper than in the lower intercostal spaces is in accord with this conclusion. In the human subjects the tricuspid component of the first sound occurred about 0.01 second after the cusps had begun to move toward the atrium.

The mechanism of this movement is probably different in patients with right ventricular hypertrophy who usually display marked exaggeration of this deflection in the left as well as in the right parasternal region. In such persons the motion may be mainly due to forward rightward twist of the heart as was described by William Harvey[8] or to a forward bulge of the right ventricular wall as is indicated by the work of Anzola.[9]

CH(S) THE LARGE LEFT PARASTERNAL INWARD MOVEMENT. All of the records from the lower intercostal spaces in the left parasternal (K) and mid clavicular (K) lines exhibited a downstroke. A similar but smaller movement was present in most of the traces from the upper intercostal spaces. This is usually the largest motion during isometric contraction (Fig. 5). It ordinarily begins 0.06 to 0.08 second after

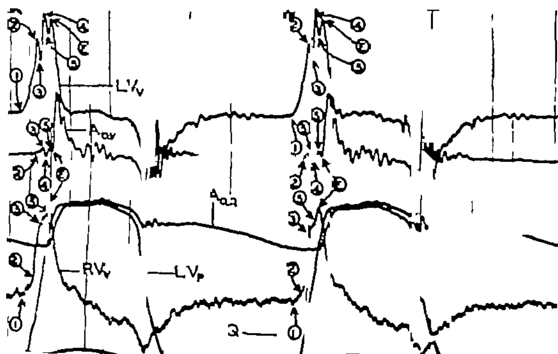


Fig. 6. Pressure velocity changes during isometric contraction in dog. Two complete cycles starting and ending at Q are shown. Time lines indicate 0.04 sec. The pressure velocity traces (v) of the left and right ventricles and of the aorta as well as the undifferentiated pressure records (p) of the aorta and of the left ventricle are shown. The greater detail of the velocity traces is illustrated. *1*. At 0.03 sec after Q. Both ventricular velocity traces begin to rise but there is soon a slight flattening of the right record. This is ascribed to an early leftward pull on the septum. *2*. At 0.06 sec after Q. As the velocity of rise in pressure in the right ventricle suddenly increases there is a corresponding decline on the left, whereas the slight rise in the aortic trace suggests backward displacement of blood with bulge of the aortic cusps. It is uncertain whether the latter factor or displacement of the interventricular septum to the right is the cause of the dip in the LV trace. *3*. At 0.065 sec after Q. The interventricular septum appears to enter into contraction causing respective rise and fall in the rate of rise in pressure in the left and right ventricles. At the same time there is a downstroke in the aortic trace indicating the first of two footward pulls on the aortic ring. This was associated with a sharp downstroke in the atrial velocity traces (Fig. 4, *arrow 4*). *4*. At 0.075 sec after Q. A second bulge of the aortic cusps probably explains the decline in the left ventricular and the increase in the aortic velocity traces. *5*. At 0.085 sec after Q. The second downstroke in the aortic velocity record associated with sharp rise in the left ventricular trace points toward a second descent of the aortic ring. *E*. At 0.09 sec after Q. Ejection of both ventricles is indicated by the sudden decrease in their pressure velocity traces and the abrupt upstroke in the aortic record.

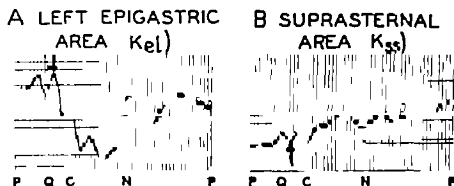


Fig 7 Headward displacement of blood at the time of mitral closure in T H a 59 year old normal male subject Paper speed 50 mm per second Traces depict one cardiac cycle starting and ending with the P wave The onsets of excitation (Q) of the carotid upstroke (C) and of the carotid incisural notch (N) are shown by the vertical lines Headward displacement of blood at 0 04 to 0 05 sec after Q is illustrated by the arrow Thus the epigastric and suprasternal records show inward and outward motion, respectively at this time This motion is designated in the text as CII(L) At 0 08 sec after Q and again at 0 10 sec A displays small upstrokes attributed to footward recoil as the two ventricles eject successively The suprasternal trace exhibits a prominence of the downstroke occurring 0 09 sec after Q and 0 03 before the carotid upstroke This motion is designated as CIII(B) and is attributed to footward pull on the aortic ring by the muscles at the base of the left ventricle

excitation starts and is greater in the lower than in the upper intercostal spaces (Table III) Corresponding deflections were not regularly encountered in the traces from right parasternal epigastric or axillary regions The suprasternal records sometimes exhibited an upstroke or a continuation of the previous one

A corresponding motion was occasionally encountered (Fig 8) but not regularly seen in the dog at this phase of isometric contraction A reciprocal ventricular relationship rise of pressure velocity on the left and fall on the right occurred earlier and has already been described [CI(l)]

Comment The observations in human subjects suggest that the movement in question is related to contraction of the interventricular septum Keith and later Grant[8] have indicated that this structure is functionally a part of the left ventricle During diastole it is rounded with rightward convexity Therefore the shortening associated with contraction pulls the septum leftward and backward If the corresponding motion occurs in the dog it either appears sooner or is masked by the rightward displacement at the time of tricuspid closure (Table II)

The outward motion in the suprasternal notch which sometimes occurred at this time is attributed to a second bulge of the aortic cusps This was reflected in the dogs by an upstroke in the velocity traces from the aorta and from the pulmonary artery (Fig 6 Table II)

If the precordial downstroke under discussion is actually the result of contraction of the interventricular septum the data in Table III suggest that the lower portion contracts before the upper This is in accord with the known sequence of septal excitation [9,11]

CII (a) SMALL INWARD RIGHT PARASTERNAL MOTIONS All of the subjects exhibited minimal downstrokes in the Kr areas at 0 075 to 0 08 second after Q (Figs 2 G and 3 C and D) Similar motions were occasionally observed in the Ks epigastric and suprasternal traces The K and K records often showed decreasing steepness of the previous large inward deflection

The dogs regularly displayed an abrupt downstroke in the left atrial record (Fig 4 arrow 4) and a smaller downstroke in the aortic traces (Fig 6 arrow 5) Similar findings were sometimes but less consistently seen in the right atrial (Fig 4 arrow 4) and pulmonary arterial record

Comment These several findings can all be explained by the assumption that

muscles which are attached to the rings of the atrioventricular and semilunar valves begin to contract at this time The motion is therefore designated as CII( ) The presence of a downstroke (signifying head ward motion of the inferior border) in some of the epigastric records would suggest that these muscles are those which pass

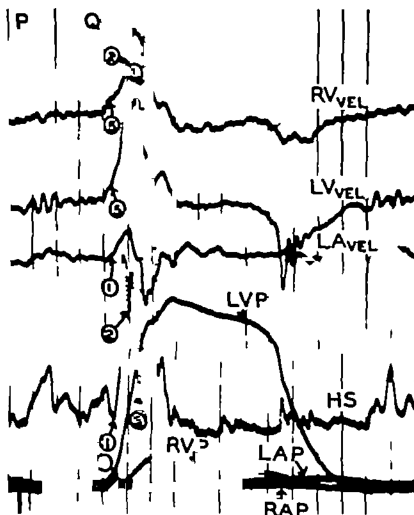


Fig 4 First heart sound in relation t pressure elocities The pressure pulse from the left (*LVP*) and right (*RVP*) entricles and the left trium (*LAP*) and right trium (*RAP*) nd the pressure elocity (dP/dt) traces (vel) from the two ventricles and from the left trium of dog are shown The heart sounds (*HS*) were recorded from the free wall of the left entricle by tech nique which depicts the intensity envelope of the sound brations (sonvelogram) Three components of the first sound are seen *1* The first major component coincides with sharp upstroke of the left atrial elocity trace and the C wa of the atrial pressure *2* The second component of the first sound associated with a phase of rapid rise in pressure in the right entricular record At the same time the right atrial velocity trace (which is not shown here) exhibited an abrupt rise The phenomena ascribed t tricuspid closure occur ery early in the course of the rise in right ventricular pre sure *3* The unusually large third component is probably an ejection sound since it occurs simultaneously with the abrupt downstroke of the left entricular elocity trace that has been associated with left ventricular ejection in all dogs in which simultaneous central aortic pressures were recorded The decrease in slope of the right entricular velocity trace labeled *S* associated with in creased steepness of the left entricular velocity trace is probably due to left ward displacement of the interventricular septum (see text)

Table I Precordial motions during the period between the onset of excitation and the start of left ventricular ejection

Movement		Description	Of 10 subjects present in	Interval to ... Q (sec)	Probable mechanism	Remarks
Terminal atrial		↗ K	10	0.003	Atrial relaxation	Frequent in other precordial areas. Often precedes Q
Initial ventricular before onset of first sound	CI(l)	↘ or ↗ K to K	10	0.017 – 0.012	Displacement of IV septum by LV	Either pull (↘) or push (↗) may predominate
	CI(pl)	↘ Upper K ↗ Lower K	5 (both)		Contraction of left (pl) and right (pr) papillary muscles	Very small, often confused by preceding and succeeding motions
	CI(pr)	↘ K	8			
First sound to right ventricular ejection	CII(I)	↗ High areas ↘ Low areas	9 (at one or more areas)	0.053	Mitral closure, backward displacement of blood	Coincides with mitral SI. Bulge of aortic cusp and of outflow tract
	CII(R)	↗ K	10	0.055	Tricuspid closure, rightward displacement of blood	About 0.01 sec before tricuspid SI. Also at K areas in patients with RVH
	CII(S)	↘ Left at K_4	10	0.068	Contraction of IV septum	Larger and earlier at lower than at upper areas
	CII( )	↘ K ↘ K KL	K 10	0.078	Descent of valve rings	Often masked in upper sternal and epigastric areas
RV ejection to LV ejection	CIII(rR)	Lower K	9	0.088	RV recoil	Often fused with later and larger LV recoil
	CIII(B)	↘ K	10	0.091	Descent of aortic annulus	Sometimes visible in carotid pulse
	CIII( )	↗ K ↘ K_4	K 10 K_4 6	0.095	Displacement of IV septum to right (?)	Also possibly bulge of tricuspid leaflets

LV Left ventricle RVH Right ventricular hypertrophy IV Interventricular

Table II Pressure velocity changes in dogs during isometric contraction

Values	Before onset of first heart sound				First heart sound to ejection				
	Gradual atrial ↘	Onset ventricular ↗	Abrupt atrial ↘	RV {↘ or less ↗} LV ↗	LA ↗ LV ↗	RA ↗ RV ↗ LV {↘ or less ↗}	A ↗ PA ↗ RV ↗ LV {↘ or less ↗}	Ao ↘ LA ↘ LV steeper ↗	A ↗ PA ↗ LV ↘ RV ↘
Number of dogs studied	RA 7 LA 8	LV 18 RV 15	LA 14 RA 14	15	13	12	Ao 6 PA 7	7	7
Number showing motion	RA 7 LA 8	LV 18 RV 15	LA 12 RA 10	14	13	12	Ao 6 PA 7	7	3 PA first 4 PA and Ao simultaneous
Average time after Q (sec)	0 01 Before Q	LV 0 02 RV 0 03	LA 0 02 RA 0 03	0 04	0 04	0 05	0 05	0 06	0 08
Probable mechanism	Atrial relaxation	LV usually begins to contract first	Contraction of papillary muscles	LV tug on IV septum	Mitral closure	Tricuspid closure Displacement of IV septum to right	Bulge of semilunar cusps	Descent of aortic and mitral rings	Ejection either RV first or simultaneous
Remarks	May start after Q			Coincides with next motion	Coincides with mitral first sound	Coincides with tricuspid first sound	Coincides with previous motion	PA only occasionally shows similar ↘	

*Only those records which were technically good were analyzed for this table. Hence the number of observations differed for different measurements. LV and RV: Left and right ventricles. LA and RA: Left and right atria. Ao: Aorta. PA: Pulmonary artery. IV: Interventricular.

Table I Precordial motions during the period between the onset of excitation and the start of left ventricular ejection

Movement		Description	Of 10 subjects present	Average time after Q (sec)	Probable mechanism	Remarks
Terminal atrial		↗ h	10	0 005	Atrial relaxation	Frequent in other precordial area Often precedes Q
	CI(l)	↘ or ↗ h to h_4	10		Displacement of IV septum by LV	Either pull (↘) or push (↗) may predominate
Initial ventricular before onset of first sound	CI(pl)	↘ Upper h_4 ↗ Lower h_4	5 (both)	0 037 ± 0 012	Contraction of left (pl) and right (pr) papillary muscles	Very small often confused by preceding and succeeding motions
	CI(pr)	↘ h	8			
	CII(L)	↗ High areas ↘ Low areas	9 (t one or more areas)	0 053	Mitral closure headward displacement of blood	Coincides with mitral SI Bulge of aortic cusps and of outflow tract
First sound to right ventricular ejection	CII(R)	↗ h	10	0 055	Tricuspid closure rightward displacement of blood	About 0 01 sec before tricuspid SI Also t h areas in patients with RVH
	CII(S)	↘ h_8 t h_4	10	0 068	Contraction of IV septum	Larger and earlier at lower than at upper areas
	CII( )	↘ h ↘ h hE	h 10	0 078	Descent of al e rings	Often masked in suprasternal and epigastric areas
	CIII(rR)	↗ Lower h_8	9	0 088	RV recoil	Often fused with later and larger LV recoil
RV ejection to LV ejection	CIII(B)	↘ h	10	0 091	Descent of aortic annulus	Sometimes visible in carotid pulse
	CIII( )	↗ h ↘ h_4	h 10 h_4 6	0 095	Displacement of IV septum to right (?)	Also possibly bulge of tricuspid leaflets

LV Left ventricle RVH Right ventricular hypertrophy IV Interventricular

Left precordial [illegible] movement†

Parasternal					*Mid clavicular*				
2nd (K[illegible])	3rd (K[illegible])	4th (K[illegible])	5th (K[illegible])	6th (K[illegible])	2nd (K[illegible])	3rd (K[illegible])	4th (K[illegible])	5th (K[illegible])	6th (K[illegible])
9	10	10	10	10	8	8	8	10	10
0 071	0 069	0 067	0 065	0 064	0 073	0 071	0 066	0 065	0 066
2 8	5 4	9 6	11 2	9 7	3 0	4 5	6 4	6 7	6 0
14 7	20 0	29 8	28 7	27 3	10 8	19 3	21 5	21 8	19 7

the two ventricles tended to eject together

Comment It is possible that this small K outward motion may represent a bulge of the tricuspid leaflets due to the rising pressure in the right ventricle However the frequent presence of a simultaneous inward deflection in the lower K₁ records suggests that the interventricular septum may now be displaced to the right as the right ventricle rapidly ejects There fore the movement is tentatively desig nated as CIII(s)

The next motion that of left ventricular recoil (Fig 2 K) signals the end of iso-metric contraction and will be discussed in a subsequent report

Discussion

The sequence of events observed in the precordial movements of man and in the pressure velocity traces of dogs exhibited certain differences One of these concerned the relative duration of isometric contrac tion in the two ventricles This was always longer for the left ventricle in the human subjects a finding which agrees with the data obtained by cardiac catheterization In the dogs this difference was inconstant and simultaneous ejection often occurred

The other difference was in regard to the deflections which are considered to indicate movements of the interventricular septum In the dog this structure appeared to be initially pulled leftward whereas the human data indicated either a leftward backward pull or a rightward forward push as the left ventricle began to contract The two later motions ascribed to the septum (con traction with leftward movement and right ward displacement) occurred in a constant relationship to the entire sequence in the human subjects but were variable in time in the dog To what extent these in consistencies are a reflection of the artificial conditions—anesthesia open chest ma nipulation of cardiac chambers—in the ani mals or represent a difference between the species is not clear from this study

Comparison of Tables I and II indicates that the similarities in the contraction sequence are much more numerous than the differences Interpretations such as these which are based on indirect methods are subject to reservation However the observation that with the exceptions men tioned each regularly occurring precordial deflection apparently had an analogue in the animals despite the use of an entirely different technique supports the validity of the interpretations

The data suggest that in both species the sequence of contraction may be ap proximately as follows The process begins in the left ventricle and in the left and right papillary muscles about 0 03 to 0 04 second after the start of excitation I

inferior portions of the two ventricles then shorten *pushing the atrioventricular cusps* headward and causing the first sound the mitral component occurring lightly before the tricuspid In the human subject the interventricular septum now contracts and moves toward the left ventricle Then those fibers (probably subepicardial) which are attached to the valve rings and which encircle the inferior margin begin to shorten The consequent tendency toward decrease in both the transverse and the vertical dimensions causes headward bulge of the semilunar and less consistently of the atrioventricular cusps Bulging of the free ventricular walls probably also occurs[6 12] but is not shown in the dogs by the techniques employed in this study and is usually masked in the human precordial traces by the large preceding (septal contraction) and succeeding (recoil) deflections *A second downward pull on the aortic* annulus by the left ventricular basilar muscles occurs either just before (dog) or after (man) right ventricular ejection As this chamber begins to empty the septum is displaced to the right

It may be noted that the spread of the contractile process from subendocardial to subepicardial fibers and from apex to base is similar to the general sequence of the spread of excitation reported by numerous investigators In the normal human being the contraction starts about 0 035 second after the beginning of excitation and almost all fibers appear to have entered into contraction by 0 105 second This duration of 0 07 second corresponds reasonably well with the average duration of the QRS complex It would seem to follow that the electromechanical lag is essentially constant in the different portions of the ventricular muscle

Some years ago Isaac Starr and associates[4] demonstrated that the destruction of the entire free wall of the right ventricle was well tolerated by dogs The evidence in the present study that the interventricular septum is displaced to the right by the higher pressure in the left ventricle may offer an explanation for this surprising phenomenon

The fundamental studies of Otto Frank Starling Wiggers and of their pupils established the important relationship between the strength of contraction and the *existing state of the ventricular muscle* immediately prior to it The natural consequence has been a tendency to use the end-diastolic pressure as a guide to the initial length and/or tension Our results suggest that this is an oversimplification While the contractile process is still spreading the pressure is rising and changes in shape are occurring As some fibers enter into contraction others are being passively stretched Both processes the increase in radius and the rise in pressure will augment the tension in the still uncontracted areas It is not necessary to enter into the long debated question of the relative importance of initial length as compared to initial tension to point out that both factors are increased in the late contracting fibers by the effects of the fibers which start the process In any case the end diastolic *pressure is a guide to the initial state of* only those fibers which contract early

The observations suggest that the concept of isometric contraction although useful and valid in relation to an entire ventricle is not strictly applicable to the *individual fiber During sequential con*traction actual shortening of some fibers occurs prior to ejection and is reflected by changes in the shape of the ventricular cavities even though the volume remains constant These conclusions are in accord with those previously advanced by Rushmer[13]

After myocardial infarction[13] and during anginal attacks[1] many patients exhibit marked bulges of the ischemic areas Aside from the weakened contraction of the directly involved muscle such bulges would appear to have an additional untoward effect When as is sometimes the case they appear during the isometric phase the shift of blood into the bulging area will reduce the radius and hence the tension of the healthy fibers

The papillary apical and right ventricular muscle bundles which contract early are thin as compared to those of the septum and of the free wall of the left ventricle which shorten later The deep bulbospiral muscle which encircles the left ventricular outflow tract and which appears to be the last of the major structures to contract is the thickest of the bundles

Other factors being equal, a given pressure will cause greater initial length and tension in the groups of thinner fibers. The sequence of contraction herein described is therefore mechanically advantageous. At the relatively low end diastolic pressure only those bundles which are thin and thus more stretched begin to shorten. As the pressure increases, the thicker but as yet uncontracted bundles are stretched. Thus their initial state becomes more favorable as regards tension and length when they finally enter into contraction. The quantitative significance of this effect needs further investigation. In any case, the hemodynamic consequences of disordered intraventricular conduction would appear to merit analysis in relation to this general concept.

It should be emphasized again that these general concepts of cardiac motion are based on tentative hypotheses derived from indirect methods. Attempts to confirm or disprove these concepts by more direct techniques are in progress.

Summary

The sequence of human precordial movements prior to ejection has been compared with the rate of alteration in pressure in the cardiac chambers and great vessels of dogs. By the latter technique, simultaneous reciprocal changes in adjacent chambers appear to provide suggestive information concerning the movements of the intervening structure. Thus, a sharp decline in the aortic curve associated with increased rate of rise in the left ventricle may signify a downward pull on the annulus of the closed aortic valve. Similar indirect evidence concerning the movements of the interventricular septum, the atrioventricular cusps, etc., was obtained and utilized as a means of arriving at a tentative interpretation of the precordial movements.

Pending evidence obtained by more direct techniques, we believe that the sequence of motions prior to ejection is as follows.

The small initial deflections appear to begin in the left ventricle and in both sets of papillary muscles. Then there seems to be headward and soon rightward motion of blood associated with mitral and tricuspid closure, respectively. This is followed by a large backward precordial movement which is assumed to be due to contraction of the interventricular septum. The next motion is a pull of the several valve rings toward the apex, producing a tendency toward shortening of both the transverse and vertical dimensions of the ventricles. At the same time there appears to be headward bulge of the still closed semilunar valves.

As the right ventricle starts to eject, three additional motions occur. These are ascribed to (1) a small forward footward recoil, (2) a second downward pull on the aortic ring, and (3) displacement of the interventricular septum to the right. When the isometric period of the left ventricle ends and its ejection begins, a larger recoil motion is seen.

According to these interpretations, the spread of contraction is similar to that of excitation. Throughout the ventricular mass the electromechanical lag appears to be relatively constant and about 0.035 second in man.

End diastolic pressure is probably an accurate guide to the initial state of only those fibers which begin the contractile process. The rise in pressure so induced stretches further the uncontracted parts and thus changes favorably the initial tension and length of the fibers which contract later.

The mechanical advantage of this process, which involves original contraction of the thinner muscle bundles and utilization of the pressure so generated to increase further the stretch and, hence, the force of shortening of the late contracting thicker bundles, is indicated.

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Model studies on the effect of the intracardiac blood on the electrocardiogram

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Although a number of experiments have been carried out on the effect of tissue inhomogeneities on the electrocardiogram, relatively little has been done on the possible influence of intracardiac blood. Measurements of tissue conductivity have demonstrated a considerably lower resistivity for blood than for other tissues. Reported ratios of blood resistivity to muscle resistivity have varied from nearly one half to one tenth.

In order to study this effect, we have carried out experiments using artificial dipoles within or adjacent to excised hearts or appropriate heart models suspended in a volume conductor. The influence of intracavitary fluids of different resistivities was estimated from leads recorded from the periphery of the tank in which heart and dipole had been submerged.

Methods

Dog hearts were used in the initial experiments. In some cases the hearts were left in situ and tubing was connected so that the test fluid would run through the cavities and back out to a collecting bottle. The dipole, consisting of two probe electrodes, was placed within the cavity or into the myocardium tangential to the endocardial wall. The thorax incision was stitched together and the dipole potentials recorded in limb and chest leads. In some experiments the hearts were excised and immersed in an elliptical cylinder model of the human thorax. Potentials were then measured from electrodes at various points on the wall of the tank. NaCl solutions were used in the tank and for the cavity test fluids. The tank fluid resistivity was 1,000 ohm-cm, and the perfusate values varied from 120 to 1,100 ohm-cm.

In later experiments[1] a small metal sphere was placed in the tank to represent the blood-filled cavity. The tank fluid resistivity was again about 1,000 ohm-cm. With this model it was possible to study the effect of the angle of the dipole with respect to the wall of the sphere and the distance between the dipole and the sphere.

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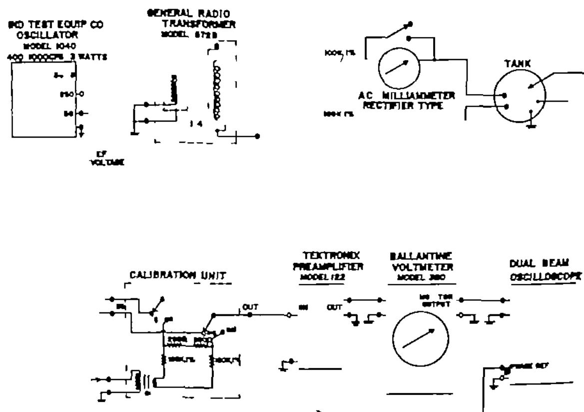


Fig. 1. Dipole-energizing and potential measuring circuits. The dipole-energizing voltage at a frequency of 400 or 1,000 cycles is obtained from the power oscillator. The oscillator voltage is stepped up to about 300 volts by the shielded transformer. High series resistors cut down the voltage across the dipole to a few volts. Constant-current feed is used, and this, in conjunction with the series resistance, eliminates the effects of electrode polarization. The tank voltages are applied through a differential amplifier to a direct reading vacuum tube voltmeter. The signal voltage is defined as being positive or negative depending on whether it is in or out of phase with a reference voltage.

on the recorded peripheral potentials. In all cases *the dipole was kept fixed, and* measurements were made with the sphere out of the tank and then at different small distances from the dipole.

Finally, these measurements were repeated using dog bladders perfused with NaCl solutions to represent the cavity.[7] A double lumen cannula was inserted into the urethra and tied in place. The two ureters were ligated. The test fluid were introduced through one tube and allowed to flow out through the other. After the bladder was filled with fluid, the double lumen cannula was clamped. Again, in studying the effect of distance, the dipole was kept fixed and the bladder moved.

The dipole-energizing and potential measuring circuits are shown in Fig. 1. Constant current dipole feed was used at a frequency of 400 or 1,000 c.p.s. *To determine phase* or polarity, the signal and reference voltages were *applied to the oscilloscope to give a* Lissajous pattern, since this was found to be the most sensitive indication.

Results

This paper describes mainly the results obtained using the dog bladder to represent the blood filled cavity. In the early experiments using dog hearts with a resistivity of intracardiac fluid about one fifth that of the tank fluid, a reduction in potentials of about 25 per cent was observed with a tangential or intracavitary dipole as compared with a homogeneous medium. The results using the metal sphere differed only in degree from the results using the bladder. The sphere corresponded to the limiting case of essentially zero resistivity for the internal fluid.

The dog hearts could be perfused by

fluids of different resistivities but had certain disadvantages. It was difficult to obtain a leak proof preparation and in some cases the resistivity of the myocardial tissue itself apparently changed during an experiment. Also it was very difficult to study the effect of the distance of the dipole from the endocardial wall or the effect of the relative dipole angle. For these reasons attempts were made to find an alternative medium having a finite value of resistivity which could be immersed in the tank. Conductive silicone rubber proved unsatisfactory because of the difference in dielectric constant between the rubber and salt solution. According to Smythe[9] if the dielectric constants of two conducting media differ and are not proportional to the conductivity an additional boundary condition must be satisfied. In this case a charge distribution is set up on the boundary.

The dog bladder proved to be an ideal solution to the problem since the problem of dielectric constants was eliminated and the cannulation of the bladder was very simple.

The positions and orientations of the dipole in the tank for each of the experiments are summarized in Table I. The x and y coordinates are defined in relation to the center of the tank. The positive values of x are toward the left side and the positive values of y are toward the front. The semimajor axis (X) is 16.0 cm and the semiminor axis (Y) is 12.8 cm. Platinum electrodes 3/[illegible] inch in diameter were mounted around the wall on a horizontal level about three tenths of the depth of the tank from the top. The depth of the fluid was 43.5 cm. Other electrodes were used to simulate the limb leads. The z coordinate in the table refers to the position of the dipole center above (+) or below (−) the circumferential electrodes. The spatial dipole angle α refers to the angle of the dipole with the horizontal plane whereas β is the angle between the projection of the dipole on the horizontal plane and the + X axis.

In the first series of experiments (with 1959 dates in Table I) the dipole used consisted of two spherical electrodes 0.43 cm in diameter with an effective inter-

Table I. Physical arrangements in 13 experiments using the dog bladder

Experiment	Location of dipole in tank (cm)			Spatial angle of dipole		Angle between dipole axis and bladder wall	Ratio of bladder to tank fluid resistivity = G	Distance of dipole center from bladder wall (mm)	Bladder volume (ml)
	x	y		α	β				
First series									
Jan 23 1959	8	3	1	0	100	0 (tang.)	0.16 1.00	10	270
Feb 3 1959	7	6.5	0	0	±180	90 (rad.)	0.16 0.96	10	200
Feb 28 1959	1.5	6.5	1	0	±180	90	0.22 0.29 1.03	10	—
March 6 1959	4	2	−0.5	0	10	90	0.14 0.33 0.61		
							0.88 1.15	10	182
April 3 1959	7.5	4.5	0	0	110	0	0.14 0.34 0.64		
							0.89 1.18	5	640
April 16 1959	3.5	2.5	2	0	135	45	0.54 0.42 0.62		
							0.95 1.23	4.5	142
April 30 1959	2	5	1	0	90	45	0.135 0.33 0.61		
							1.00 1.24	4.5	250
May 8 1959	5	3	1	0	110	30	0.13 0.31 0.57		
							0.90 1.18	3	390
Second series									
Jan 8 1960	10	3	2	0	100	0	0.15	2 7 12	—
Jan 9 1960A	5	5	0	0	0	90	0.135	2 to 42	—
Jan 9 1960B	5	5	0	0	−90	0	0.15	2 to 31	—
Feb 3 1960	6	3	0	0	35	45	0.15	2 to 32	—
Feb 4 1960	3	7	−3	30	60	45 60	0.145	2 to 52	—

[illegible]

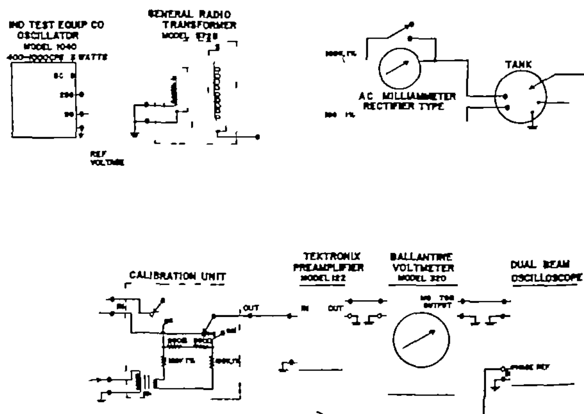


Fig. 1. Dipole-energizing and potential measuring circuits. The dipole-energizing voltage at a frequency of 400 or 1,000 cycles is obtained from the power oscillator. The oscillator voltage is stepped up to about 300 volts by the shielded transformer. High series-resistors cut down the voltage across the dipole to a few volts. Constant-current feed is used, and this in conjunction with the series-resistance eliminates the effects of electrode polarization. The tank voltages are applied through a differential amplifier to a direct reading vacuum tube voltmeter. The signal voltage is defined as being positive or negative depending on whether it is in or out of phase with reference voltage.

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The dog hearts could be perfused by

tivities are expressed in terms of the parameter G which is equal to the ratio of the resistivity of the fluid in the bladder to the resistivity of the tank fluid In another experiment a tangential dipole used in conjunction with solutions of five different resistivities gave the results shown in Fig 3 Dipoles with intermediate angles (Fig 4) gave curves intermediate to those shown in Figs 2 and 3

The question arises as to whether it is desirable to show the effect of different bladder fluid resistivities on the distribution of the wall potentials by plotting for each point the ratio of the potential obtained with the low resistance fluid to that obtained with the high resistance fluid the latter corresponding to a homogeneous medium In some cases this was not practical since if the curves under comparison do not have the same zero potential points on the wall i e if there is a shift in the null axis the ratio must have the values of zero and infinity at these two points An alternative way to express the effect is in terms of the change in potential at each point Such incremental curves do not go to infinity at any point Furthermore calculation in terms of ratios may create a false impression when small potential values are involved For example if there is a change in the potential from 0 02 to

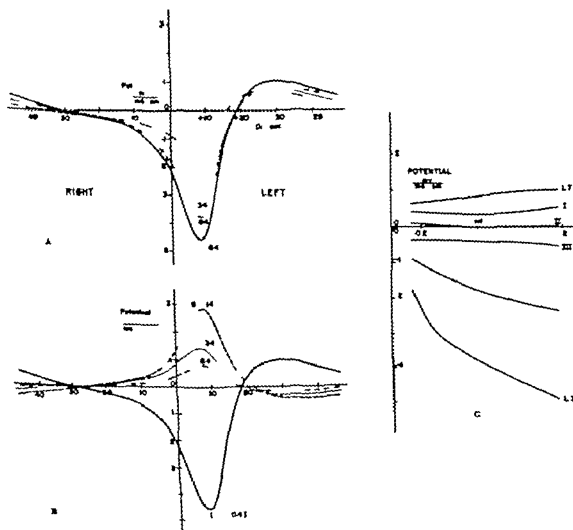


Fig 3 Tank potentials as function of resistivity ratio for tangential dipole *A* shows the actual ci ferential distributions and *B* shows the potential-difference curves *C* shows the variation in potential bipolar limb leads and three wall points Lower al produce general decrease in potentials

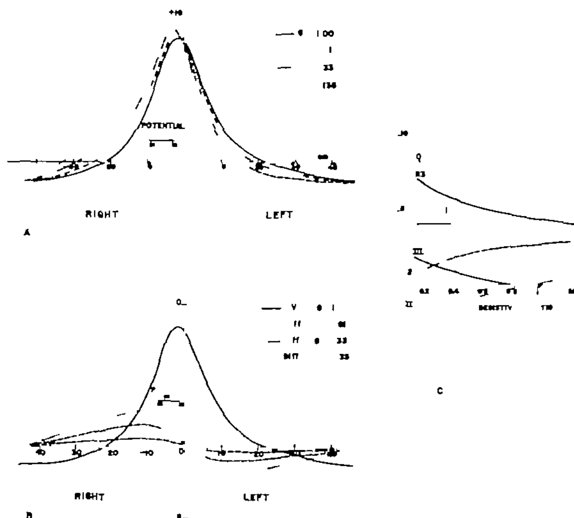


Fig 4 Tank potentials as a function of resistivity ratio for dipole at an angle of 45 with the bladder wall As G is lowered the potential increase in some regions and decrease in others

0 04 mv this would correspond to a ratio of 2 0 The difference between these potentials on the other hand is 0 02 mv a fact which may be given its proper perspective In addition the incremental curve gives the actual change in millivolts produced by the experiment and can be expressed analytically as the difference between two distributions of potential

Plots were made showing the difference between the potential distribution curves for the high resistivity fluid (representing the case of a homogeneous medium) and those for the fluids of lower resistivity used These are shown in Figs 2 B 3 B and 4 B In these figures the actual distributions of potential for the homogeneous cases are also plotted for purposes of comparison The other curves then show the potential which must be added to obtain the actual potential for the lower bladder fluid resistivity experiments In addition curves were plotted showing some of the wall and limb potentials as a function of the resistivity ratio G as shown in Figs 2 C 3 C and 4 C

With the dipole arranged radially it is evident (Fig 2) that the magnitude of the wall potentials became greater as the resistance of the bladder fluid was lowered (smaller values of G) The magnitude of the limb lead potentials was also increased but the calculated Einthoven angle changed

only from +5° to −4 In the wall potential distributions there is a common or crossover point at which the potential is the same for all values of resistivity ratio This point is located about 3 cm to the left of the center line This point does not coincide with the intercept of the transverse axis with the wall since this is at 5 5 to 6 9 cm to the left of the center line depending on G The significance of this point if any is not known

With tangential dipoles the potential distribution curves (Fig 3,A) also show the expected results As the resistivity of the bladder fluid was decreased the magnitudes of the wall potentials were generally decreased a change opposite to that observed with a radial dipole Again a crossover point exists In the experiment shown in Fig 3,A this point is at 23 cm which coincides with the lateral center of the tank In this experiment the potential of the limb leads changed very little These potentials were small since the limb leads in this case were near the dipole null axis In another experiment (Jan 23 1959) all the lead potentials were decreased whereas the Einthoven angle changed only by 8°

Fig 3 shows that the potentials were *increased* by the low resistivity fluid over a small region on the left side Similarly with the dipole oriented radially the potentials measured at the wall a little to the left of the midline were decreased by low resistance fluids Both these observations were restricted to small areas and are opposite to the general trend of the changes observed in all other regions

With dipoles at an angle of 45° to the bladder wall (Fig 4) the magnitude of the maximum negative potential increased as the bladder fluid resistivity was lowered but the magnitude of the maximum positive potential decreased Thus the 45° dipole gave results intermediate between the radial and tangential dipoles The difference curves show that potentials were made more negative on the left side and more positive on the right side The potential-difference curves show this effect very clearly The value of α_F was not computed for this case since the dipole was normal to the frontal plane

With the dipole at 30° the results were similar to those obtained at 45° but the changes were less marked In this case the difference curve also showed that as the resistivity of the bladder fluid was lowered the potentials became more negative over part of the wall and more positive over the remainder

Tests with the bladder out of the tank gave values which were practically identical to those obtained when the same fluid was used in the bladder and tank (G = 1 00) Slight differences of the order of 1 per cent were observed and these might have been due to the possible lower resistivity of the bladder tissue itself

2 *Dipole at various distances* In the second series of experiments (Table I) the bladder fluid resistivity was maintained

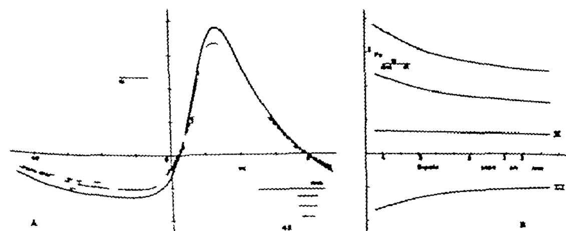


Fig 5 Potentials as function of the distance between radial dipole and the bladder wall The ratio of bladder fluid resistivity to tank fluid resistivity = 0 15

constant at 140 to 150 ohm-cm, corresponding to an outside to inside ratio of resistivities of 6 to 7. Measurements were made with the dipole at various distances from the bladder wall ranging from 0.2 to 4 cm. This would simulate the condition in the heart when the excitation wave travels from the endocardial to the epicardial layers. In practice the dipole was kept stationary in the tank and the bladder was moved relative to the dipole. Thus the bladder-dipole distance was changed while the dipole position and its orientation relative to the tank wall remained constant. This was done in order to avoid the field changes which would result from movement of the dipole alone.

Results from a representative experiment with a radial dipole at eight different distances are shown in Fig. 5. With a radial dipole the potentials were generally increased in magnitude as the bladder was brought closer to the dipole (Fig. 5,*A*). A separate graph was made of the variation of the peak potential on the left side and the bipolar limb leads as a function of distance between bladder and dipole (Fig. 5,*B*). For the first centimeter the slope of the peak potential curve is essentially constant. After this the slope gradually becomes smaller so that the same increment in separation has less effect at greater distances than when the dipole is closer to the bladder. The limb lead potentials increased by varying amounts as the bladder was brought closer to the radial dipole, although Lead II remained constant. The Einthoven angle changed only by [illegible]° however.

Tangential dipoles resulted in opposite changes. As the bladder was brought closer to the dipole the magnitude of the potentials decreased. A graph of the peak potential as a function of dipole bladder separation shows that in this case also the slope is constant for the first centimeter and that after this the rate of change decreased. Similarly, as the bladder was brought closer to the dipole all limb lead potentials decreased. In Experiment Jan. 9, 1960B, the peak wall potential dropped from 2.1 to 1.1 mv./ma.-cm.

Dipoles at intermediate angles produced opposite changes at different measuring points. With a 45° dipole (Experiment Feb. 3, 1960) *bringing the bladder close* to the dipole increased the potentials over the right side to the right of a point 7 cm. from the center line and over the left side from a point 6 cm. to the left of the center line. Between these two points, at the front center region of the tank, the potentials were made more negative. In addition, at such intermediate dipole angles there was a greater *shift of the null points* than occurred with strictly radial or tangential dipoles. Also the slope of the maximum potential curve was not constant over the first centimeter. However, in a study of the *effect of distance the* bladder was displaced radially from the dipole so that the relative angle at greater distances may have been altered. The changes in the limb leads were as follows: V_L 0.22 to 0.76; V_R −0.28 to −0.80; V_F 0.16 to 0.15; I 0.50 to 1.57; II 0.44 to 0.95; III −0.07 to −0.62 (all values in millivolts per milliampere-centimeters). The first value given is for the bladder removed completely from the tank. The second value in each case is for the dipole 2 mm. away from the bladder. α_F changed from 23° to 7°, and since the correct value was 0°, the effect of the low resistance fluid in this experiment was apparently to offset the inherent error in the Einthoven triangle method.

In the last experiment shown in Table I the dipole made an angle of 30° with the horizontal plane as well as an angle of 60° with the frontal plane. As the bladder was moved away from the dipole in a horizontal line, the angle between the dipole axis and the bladder wall changed considerably. Comparing only the potentials with the dipole out of the tank with those obtained when the dipole was nearest the bladder, we found that at the center and on the right side the potentials increased in magnitude. The electrode at the center of the front of the tank, for example, changed from −0.5 to −2.4 mv./ma.-cm. The electrode 3 cm. to the left of the center line changed from +0.6 to −1.4. The next electrode changed from +1.8 to 0.9 mv./ma.-cm. This amounted to a decrease in positive magnitude but was a change in the negative direction similar to that of the leads farther to the right. The electrode 9 cm. to the left decreased only by 0.06 *and the next electrode increased from*

+1 68 to +1 95 mv/mm cm Leads II and III both increased from +1 04 to +2 06 and from +0 34 to +1 17 respectively Lead I changed less from +0 0 to +0 90 The projected angle α_F changed from 49° to 64° Although the dipole made an angle α of only 30° with the horizontal plane the angle between the projection of the vector on the frontal plane with the +X axis α_F is different because the vector is not in the frontal plane The projected vector α which is found in the Einthoven triangle system is given[1] by

$$\tan \alpha_F = \frac{\tan \alpha}{\cos \beta} \quad (1)$$

From this with $\beta = 60°$ the value of α_F is 49 In this experiment therefore the Einthoven method gave the correct value for α_F in the homogeneous case and the effect of the bladder was to cause an incorrect value as calculated from the measured limb potentials

Discussion

The results clearly confirm the theoretical conclusions[1] that the effect of a highly conducting medium on an adjacent dipole is to enhance the potentials due to radial dipoles to diminish those due to tangential dipoles and to cause an increase or decrease in potential at different field points if the dipole angle is intermediate They also show that the magnitude of the effect depends on the distance of the dipole center from the conducting mass The significance of these results in electrocardiology depends therefore on the time course of the activation of the heart i e the direction and position of the effective dipoles relative to the cavities

It is generally agreed that atrial depolarization begins with impulse formation in the sinoatrial node which spreads as a wave through both atria in the direction of the atrioventricular node This depolarization wave front is relatively unopposed and for the most part is longitudinal with respect to the atrial cavities This spread of excitation is the counterpart of an experimental tangential dipole for any point in time The P waves must be substantially reduced by the shunting action of the blood With hypertrophy of the atrial wall one might expect the excitation wave to assume a more oblique or radial angle with respect to the atrial cavity This would then represent an experimental dipole with a more radial orientation and the surface electrocardiogram would record a P wave of increased voltage

Ventricular depolarization is of course much more complex It has been stated by several authors that the initial excitation begins at the termination of the left bundle on the left side of the septum From this point there is a rapid tangential spread through the endocardial layers terminating in the posterior wall of the left ventricle at the base of the heart Subsequent activation of the myocardium is apparently in a transmural direction even though the time sequence of activation is from apex to base It has been stated that in the human ventricle the endocardial layers seem electrically silent in respect to the formation of the R wave in the electrocardiogram[11] The only deflection these investigators were able to record from the endocardial musculature consisting of one third to one half of the thickness of the left ventricle was a QS deflection Perhaps pertinent to these observations is the tangential nature of endocardial excitation and its proximity to the blood filled cavity Surface potentials as represented by R wave deflections may be significantly reduced As the spread of depolarization shifts to that represented by a radial dipole that is to say from endocardium to epicardium the ECG components should be increased As the excitation proceeds toward the epicardium the relative increase would be less because of the increasing distance from the cavity The final apex to base epicardial vector on the left ventricle would not be changed greatly Potentials due to effective dipoles spreading from the endocardium at an oblique angle with the cavity wall would be enhanced at some regions of the body and diminished at others

If one considers the individual dipole components of excitation rather than the over all resultant the picture becomes still more complicated If radial and tangential or intermediate dipoles existed fairly close together the contribution of each to the summation would vary In either case the observed magnitude and direction of t

heart vectors as determined from surface measurements would be different from the true values

The data show that if the ratio of the resistivity of the myocardial tissue to that of blood is as high as only 4 or 5 the effect of the intracardiac blood on adjacent dipoles must be significant If the resistivity of the external medium surrounding the heart is still higher the effect will be enhanced

Summary

Perfused dog bladders to simulate the intracardiac blood mass were placed in an electrolytic tank in the shape of an elliptical cylinder An artificial dipole was placed adjacent to the preparation and wall and limb potentials were measured Measurements were made with the dipole axis tangential radial or at intermediate angles to the bladder wall In one group of experiments the leads were measured for ratios of bladder fluid to tank fluid of from about 0 14 to 1 20 In the second series of experiments the ratio was kept constant at 0 15 and field potentials were measured a a function of the distance between the dipole and the bladder The results show that the contribution of a dipole component to the potential at a given electrode depends on the ratio of the resistivity of the blood to the resistivity of myocardial and thorax tissue the distance of the dipole from the cavity its direction relative to the cavity wall as well as on the orientation of the dipole with respect to the electrode

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An orthogonal lead system for clinical electrocardiography

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Einthoven, in his early investigations of the electrocardiogram, was concerned with the influence of the orientation of the heart on the form of the complexes. His interest in this relationship led to the introduction of the concepts of the manifest vector and the Einthoven triangle. These concepts are two dimensional in character and apply to the frontal plane. Despite this limitation, they have proved to be so useful that they are routinely employed in electrocardiography today.

The value of Einthoven's approach has been so evident that the possibility of extending it to include all three components of the manifest vector has been under consideration for many years. There are several reasons why the early research with this objective has not culminated in clinical application. The Einthoven triangle itself had for many years no clearly demonstrable scientific basis. This basis has since been provided by the concept of the lead vector introduced by Burger and van Milaan. Another problem has been that of obtaining the sagittal component of the heart vector from potentials induced in electrodes on the chest close to the heart. The recently developed "lead field" concept has shown that the proximity effects can be suppressed through the use of several electrodes whose potentials are averaged.

Still another obstacle has been the difficulty of determining the electrical axis in three dimensions without burdening the clinician with calculations of inordinate mathematical complexity. An answer to this problem is the use of "resolvers," electronic instruments introduced by Schmitt and studied by several other investigators.[4] It has been shown[5] that the approximate mean electrical axis of the QRS and T complexes can easily be determined with these devices. These instruments can be built as compact and reliable units well adapted to the clinic.[6]

Because of these relatively recent developments, it is now possible to determine the electrical axis of the heart in the clinic in three rather than two dimensions. All that is required is a lead system which provides the three components of the heart vector.

A great number of such orthogonal lead systems have been proposed, each with merits and deficiencies of its own. It is beyond the scope of this article to review each of them. In our opinion, even the best systems, such as Schmitt's[7] and Frank's,[8] do not strike the optimum balance between accuracy and simplicity.

In this report an orthogonal system is described which is intended to satisfy clinical requirements. It is designed specifi-

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cally for determining the electrical axis of the heart on a routine clinical basis. It represents a carefully drawn compromise between the simultaneous need to maximize accuracy and to minimize complexity. The system has been subjected to quantitative studies aimed at finding the optimal configurations and number of electrodes, the optimal electrode spacing, the relative sensitivities of the leads, the influence of variations in body shape, the effect of the electrical heterogeneity of the trunk, and the error resulting from misplacement of the electrodes.

The report is divided into two parts. Part I describes the system in detail and is intended for the clinician who desires detailed instructions as to the placement of the electrodes and connections to the electrocardiograph. Part II outlines the various studies of the system which have been made and is intended primarily for the research worker who is interested in the concepts and measurements on which it is based.

Part I The axial system

Lead connections for human subjects. Fig. 1 shows a diagrammatic sketch of the location of the lead electrodes and the connections between them. The photographs of a human subject in Fig. 2 also demonstrate the position of the electrodes. The electrodes are paired together and form *three leads, each electrode group symmetrically* arranged about an axis which passes through the center of the heart. The axes thus formed are oriented in the longitudinal (head to toe), transverse (left to right), and sagittal (front to back) directions, respectively. It is because of these three mutually perpendicular axes that the electrode configuration is referred to as an "axial" lead system. The reference directions for all leads are taken so as to give predominantly upward deflections with normal subjects.

A. LONGITUDINAL LEAD (Y AXIS). The longitudinal lead is taken between an electrode on the left leg and a second electrode attached to the left side of the neck. The connections to the amplifier are such that an upward deflection will occur when the leg is electrically positive relative to the neck.

B. SAGITTAL LEAD (Z AXIS). The sagittal lead is taken between three electrodes on the chest and a fourth electrode on the back. The potential of the chest electrodes is averaged by means of three 100 000 ohm resistors. Precision resistors ($\pm$ 1 per cent) should be used.

The chest electrodes form an equilateral *triangle so oriented that its base is nearest* the subject's feet. For subjects whose height lies in the range of 170 $\pm$ 30 cm. (4 feet 7 inches to 6 feet 7 inches) the electrode centers are located *6 cm.* from the center of the triangle. For children and small adults it is desirable to change spacing of the chest electrodes. The spacing in their case should be directly proportional to height. For example, for a child of one half the reference height of 170 cm., i.e., 85 cm., the spacing between the center of the electrodes and the center of the triangle should be 3 cm. The back electrode lies directly behind the center of the chest triangle.

The center of the triangle should, in theory, be directly above the center of gravity of the ventricles. In practice the exact location of this point is exceedingly difficult if not impossible to determine. However, anatomic, radiologic, and electrocardiographic data indicate that the point on the chest in the fifth intercostal space 2 cm. to the left of the sternal margin is approximately over the center of gravity of the ventricles. The center of the triangle should be placed at this point except in such cases as dextrocardia,* wherein the center of the heart obviously differs substantially from the position specified above.

The sagittal lead is connected so that an upward deflection occurs when the back is electrically positive relative to the chest.

C. TRANSVERSE LEAD (X AXIS). The transverse lead is taken between two electrodes on the left side and a third on the right. The potential of the left electrodes is averaged with two 66 000-ohm resistors. (Any resistance value between 60 000 and 70 000 ohms is satisfactory, but it is necessary that the resistors be equal.) Precision resistors ($\pm$ 1 per cent) should be used. The right electrode lies at the same longitudinal

*In dextrocardia the electrodes should be placed on the right leg and right neck rather than the left.

level as the center of the electrode triangle on the chest. It is located on the right side one third of the way from the chest to the back. For example, if the depth of the chest is 18 cm, the electrode should be located 6 cm from the plane of the anterior chest wall and 12 cm from the plane of the back. The electrodes on the left side should also be located one third of the way toward the back at longitudinal levels 5.5 cm above and below the level of the center of the chest triangle. The electrode spacing is therefore 11 cm. If the spacing of the chest electrodes is changed, the spacing of these side electrodes should be changed by the same factor. For example, if the chest electrodes are located 3 cm rather than 6 cm from the center of the triangle, then the side electrodes should be located 2.75 cm rather than 5.5 cm above and below the heart level.

The transverse lead is connected to the amplifier so that an upward deflection occurs when the left side is electrically positive relative to the right.

Lead connections for dogs. The lead system proposed for dogs is shown diagrammatically in Fig. 3. It is identical to the one

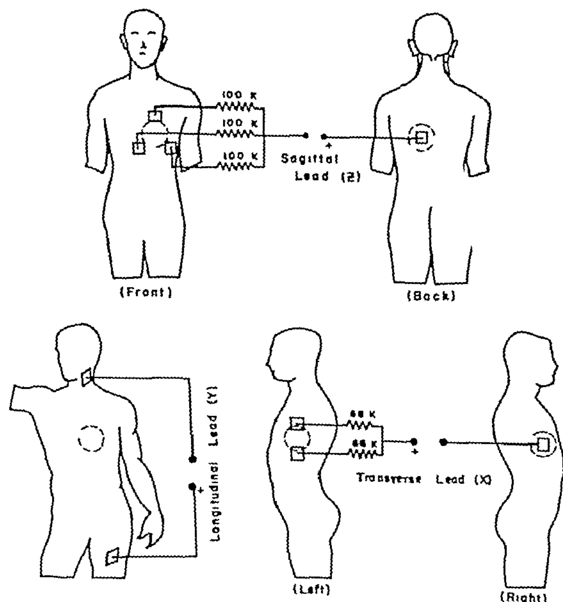


Fig. 2. Location of axial leads.

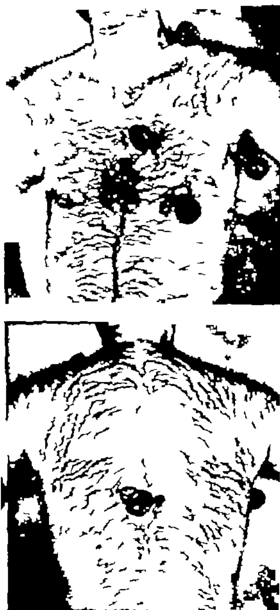


Fig. 2. Subject with electrodes in position.

used for human subjects except that there are two electrodes on the right side rather than one. The relatively narrow chest of dogs and the central location of the dog's heart required this change. The spacing of the electrodes on the sides and the chest remains as in the system for human subjects. The center of the triangle formed by the three chest electrodes is placed directly over the sternum.

Amplifier sensitivity. The voltages from all of the three leads should be recorded with the same calibration, i.e., some specified deflection per millivolt.

Electrodes and electrode placement. Suction electrodes have proved to be quite adequate for this lead system and are recommended for all electrode sites except those of the left and right legs, left neck, and back. (The right leg electrode is the "ground.") Strap electrodes are more suitable for the legs. Either a suction or a strap electrode can be used on the left neck. The back electrode can be a flat plate on a flat rod held in place by body pressure, or a suction electrode.*

Time can be saved in placing the electrodes through the use of the Lucite template shown in Fig. 4. An efficient procedure for electrode placement is the following: (a) Determine and mark with a crayon the point in the fifth intercostal space 2 cm. to the left of the left sternal margin. (b) Center the chest template on this point with its base toward the subject's feet and mark the subject with a crayon through the three holes in the template. (c) Place the template on the left side and mark points one third of the way from chest to back at the longitudinal levels 3.5 cm. above and below the center of the chest electrodes. (d) Place suction electrodes over the five marks on the left side and chest. Place a suction electrode on the right side one third of the way from chest to back at the same longitudinal level as the center of the chest triangle. Place the electrode on the back directly behind the center of the chest triangle. Place a suction or strap electrode on the left neck. (e) Place strap electrodes on the two legs. (f) Connect electrodes to the box containing the averaging resistors.

Cables and connector boxes. Fig. 5 shows the wiring diagram for a one-channel electrocardiograph. The wiring diagram for a three-channel electrocardiograph is identical except that the switch and the 33,000 ohm resistor are removed. The shielding and grounding arrangements shown are intended to minimize the possibility of 60 cycle interference. The cables must be securely anchored to the connector box in such a fashion that frequent flexing of the cables does not lead to open or short circuits.

*It is recommended that the suction electrode on the back be of the relatively flat type with a long tube between the electrode and the suction bulb.

The extra 33 000-ohm resistor shown in the longitudinal lead in Fig 5 prevents a slight increase in sensitivity occurring when this lead is taken with an electrocardiograph having a relatively low input resistance (1 500 000 ohms or less) The resistor is not needed with electrocardiographs having an input resistance greater than this value

If desired the averaging resistors for the electrodes on the chest and the left side can be placed near the end of the cables rather than in the connector box If this is done the resistors must be shielded and great care taken to insure that flexing of the cables does not cause open or short circuits

Part II Design of the system

The selection of an orthogonal lead system for use in electrocardiography is a problem in design rather than a subject for scientific investigation There is no unique answer In fact there is an infinite number of solutions none subject to exact analysis and each of which represents an attempt to obtain some sort of optimal compromise between a variety of conflicting requirements The axial lead system described here represents an attempt to achieve such an optimum

Data for the design of the system have been obtained from three sources a homogeneous model of the human body mathematical models and live human subjects Measurements from live subjects sometimes differed significantly from those obtained with homogeneous models The relatively low resistance of the surface musculature appears to account for most of these differences

The configuration adopted for the electrodes has several desirable features The electrodes on each of the six sides of the body form three orthogonal axes If the position of the heart is known they can easily be located so that these axes pass through the heart center An advantage to the use of multiple electrodes on the left side and chest (areas close to the heart) is that they tend to eliminate proximity effects Use of multiple electrodes also makes the lead less sensitive to errors in electrode position This point is illustrated schematically in Fig 6

That proximity effects are indeed small was demonstrated by comparing the voltage of these leads with voltages of ideal leads composed of many electrodes effectively covering the entire surface of the body The sagittal ideal lead for example employed 19 electrodes on the

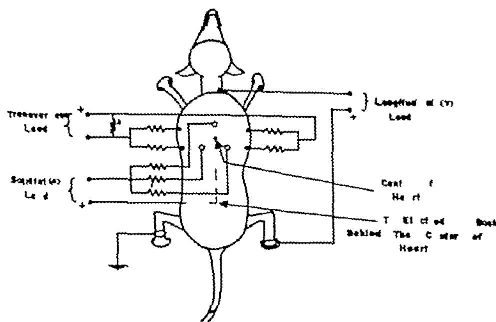


Fig 3 Location of dog leads

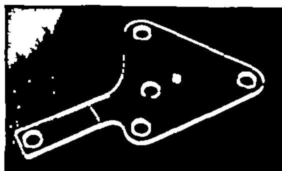


Fig. 4. Oblique view of template used to mark location of electrodes. The hole in the center of the triangular section is 6 cm. from the holes in the corners of the triangle. The hole at the end of the handle is 11 cm. from that which lies just within the triangular area.

chest and stomach and 16 on the back. Eighteen records obtained from six subjects showed that the forms of the voltages in the axial and ideal leads were so similar as to be effectively indistinguishable. The only important difference noted was one of amplitude.

The spacing of the lead electrodes was established by experiments with the tank model. The spacing chosen gives the most uniform field in the heart region of the tank.

The relative sensitivities of the leads were obtained first with a tank of dimensions and shape similar to those of the average human body. The tank was filled with tap water. The sensitivities of the transverse and longitudinal leads were found to be equal, whereas the sensitivity of the sagittal lead was 20 per cent greater.

A check on this method was made by comparing the relative amplitude of the voltages in the axial and ideal leads. From the known cross-sectional area of the latter the absolute strength of the lead field (amperes per square meter) could be determined under the assumption that the lead field was uniform. The known relative amplitudes of the axial lead voltages then allowed their lead fields to be estimated in turn. Studies of six subjects indicated that the transverse and sagittal leads have equal sensitivity, whereas that of the longitudinal lead is 25 per cent greater. The difference between this result and that obtained with the model could be attributed to shunting

Electrodes
Shielded Cable
To Electrocardiograph
Electrocardiograph
66 k
100 k
L
S

Fig. 5. Wiring diagram for single-channel electrocardiograph.

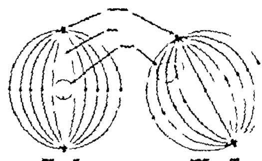


Fig 4 Lead field of axial and non axial leads Note that the field of the axial type will change considerably less than that of the non axial type when the relative position of the heart and electrodes is altered

of the lead field by the low resistance layer of muscle directly under the skin

The effect of the relatively low resistance of the heart blood mass on the sensitivity of the leads was also investigated Reflections by the chest surface of perturbations of the lead field produce a decrease in the sensitivity of the sagittal lead and a smaller decrease in the sensitivity of the transverse and longitudinal leads These changes were estimated mathematically by representing the heart as a homogeneous sphere in an otherwise homogeneous semi infinite conductor of three times the heart s resistivity A decrease in the relative sensitivity of the sagittal lead of roughly 5 per cent was computed

An average figure for the lead sensitivities has been adopted Accordingly the sensitivities (and hence weighting factors) of the three leads have been made equal

The influence of variations in body shape on the sensitivities of the leads was also investigated A box shaped tank model with movable glass sides was used for this purpose These studies showed that significant changes in sensitivity from the average occurred mainly in those subjects who had slender flat chests Here the sensitivity of the sagittal lead increased by as much as 30 per cent The sensitivities of the other leads increased also The effect is similar to that produced by ventricular enlargement It does not seem that the changes are in general large enough to justify custom tailoring of the leads to each individual subject Nevertheless the clinician should be aware of the augmentation of lead voltages which occurs in subjects with long thin chests

A study was made to determine whether substantial changes in resistivity within the heart could prevent the axial lead system from compensating for variations in heart orientation Theoretical analysis indicated that they would not since the heart s dipole moment as seen from a remote point will rotate with a mechanical rotation of the heart An experimental check of this was made by constructing an assembly whose resistance differed drastically from that of the tap water of the tank model in which the assembly was immersed A dipole fixed to this assembly was activated for each of six orientations of the structure The changes in orientation were counteracted by an electrical counterrotation (using the resolver principle) of the voltages induced in the axial leads Almost perfect compensation was achieved in every case This demonstrated that differences in resistance of heart muscle and blood and anisotropy of the muscle would not prevent the dipole moment of the heart s field from being determined even though an interpretation of this moment as the vectorial sum of the heart s electromotive forces would be inaccurate

The sensitivity of the axial lead system to changes in the location of the electrodes was determined by a comparison of voltages induced in two identical leads displaced from one another in a longitudinal direction In eight normal and nine abnormal subjects a 5-cm displacement of the axial lead electrodes produced an average difference voltage of 10 and 22 per cent respectively of the transverse and sagittal lead voltages For comparison the Frank lead system was investigated under identical circumstances and yielded voltage differences averaging 25 and 33 per cent respectively for its transverse and sagittal leads

These experiments also showed that the smallest changes occurred in the lead voltages as a result of errors in electrode placement when the fifth intercostal space was used as the reference level for the transverse and sagittal leads This finding is in agreement with anatomic and radiologic data regarding the position of the ventricles

Conclusion

Although the investigation of the axial lead system is continuing we believe that enough work has been done to warrant its recommendation to clinicians who have need of a set of orthogonal leads. The studies reported have shown that the axial lead voltages are almost identical in form to those obtained with "ideal" leads using large numbers of electrodes. In addition they have shown that the system is not unduly sensitive to variations in body shape or errors in electrode location. All evidence gathered thus far indicates that the system provides a reasonably adequate means of determining the three orthogonal components of the dipole moment of the heart's electrical field.

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The atypical systolic murmur of minute ventricular septal defect and its recognition by amyl nitrite and phenylephrine

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An unusual systolic murmur characteristic of very small ventricular septal defects has been investigated in 12 patients. It is a short crescendo-decrescendo murmur which terminates well before the second heart sound. Since it resembles an ejection systolic murmur[1] and is unaccompanied by abnormal clinical, electrocardiographic, or radiologic signs, ventricular septal defect may escape consideration in the differential diagnosis.

Because no reference is made to this type of murmur in many recent papers on the ventricular septal defect, we thought it worth while to draw attention to it and the methods used in the diagnosis of very small septal defects. Although other authors[2-4] have stated that occasionally the murmur may be short in small septal defects, Leatham was, to our knowledge, the first to suggest that a short murmur confined to early systole may be produced by a defect *in the muscular septum*. The short duration was attributed to closure of the defect when the ventricle is fully contracted.

It is the thesis of this paper that simple auscultation aided by amyl nitrite and phenylephrine[5] is the most sensitive clinical method of diagnosing these defects.

Material and methods

Twelve patients with loud short crescendo-decrescendo murmurs were studied because the response to *amyl nitrite and phenylephrine* strongly suggested an atypical ventricular septal defect. Eight patients were catheterized.

Amyl nitrite was administered to all patients and phenylephrine to most, and the changes in the murmur and heart sounds were always confirmed by recording sound tracings at fast paper speed according to the techniques previously described.[5] The tests were repeated during cardiac catheterization in order to correlate the change in murmur with simultaneously recorded left-sided and right-sided pressures and dye-dilution curves obtained before and at the peak responses to amyl nitrite and phenylephrine. By this means the change in murmur could be correlated

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Fig. 1. Case 5 W. M. Dye-dilution curves and sound tracings before and after phenylephrine in the smallest ventricular septal defect studied. The dilution curves obtained at the brachial artery after injection of 2.5 mg. of Cardiogreen into the pulmonary artery show no evidence of left-to-right shunt before (not shown) and after phenylephrine. But the sound tracing reveals great intensification and lengthening of the unusually short crescendo-decrescendo murmur, strongly suggesting a small ventricular septal defect. Dye-dilution curves obtained from the right heart after injection of 2.5 mg. of Cardiogreen via a second catheter in the distal pulmonary artery reveal a doubtful left-to-right shunt in the main pulmonary artery and high right ventricle, but only after phenylephrine is the shunt convincingly shown. Note the delayed circulation time caused by phenylephrine. The curve from the right atrium was recorded after phenylephrine had largely worn off; there is no left-to-right shunt at this site. The small dots measure milliliters of blood flow through the densitometer. (The unusual appearance of the murmur after phenylephrine is due to capacitance overloading of the tape recorder by the unexpectedly great intensification.)

with the change in pressure gradient and precentage shunt flow.

The diagnostic procedure used for the detection of small left to right shunts was as follows. Routine catheterization was performed using a Waters cuvette oximeter for direct oximetry of multiple samples of blood taken in rapid succession from various sites in the heart. Dye-dilution curves were recorded at a systemic artery after injection of Cardiogreen into the right side of the heart using a Norman cuvette densitometer and a Honeywell recorder. The curve was repeated during the peak pressor effect of phenylephrine, which was given with the object of eliciting or accentuating a left to right shunt.

The technique employing two venous catheters was used whenever the above mentioned method failed to detect a shunt. Dye-dilution curves obtained from the proximal pulmonary artery, high and low right ventricle, right atrium, and superior vena cava after the injection of Cardiogreen into the distal pulmonary artery enabled detection of trivial shunts and their localization to the ventricle.[3] Phenylephrine was again used to increase the shunt. The magnitude of the shunt was determined by relating the area of the abnormally early appearing deflection in the right ventricle to the area of the dilution curve recorded at a systemic artery after injection into the right heart. Two assumptions were made, namely (1) that the cardiac output did not change between the recording of the venous and arterial dye-dilution curves and (2) that the area of the systemic arterial curve would not be significantly different from that of the curve recorded in the pulmonary artery after injection into the superior vena cava in view of the very small shunt.

The phonocatheter was then used to

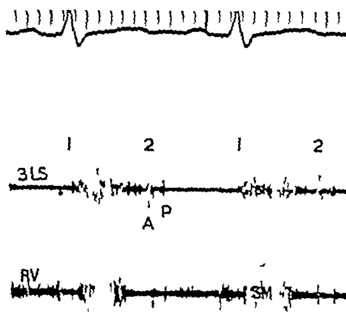


Fig. 2. Case 1, T. A. The synchronously recorded external (3LS) and intra-right ventricular (RV) sound recordings reveal short, loud, high frequency, crescendo-decrescendo murmurs of identical shape, proving that the typical externally recorded murmur which appears to be an ejection murmur is truly representative of the non-pansystolic murmur generated within the right ventricle by an interventricular septal defect. Amyl nitrite and phenylephrine softened and intensified both murmurs respectively. There was a softer lower frequency physiologic ejection murmur in the pulmonary artery and no murmur in the right atrium.

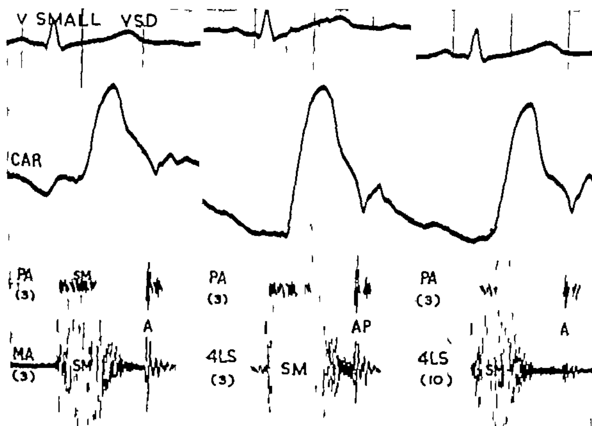


Fig 3 Case 4 L D The early systolic crescendo-decrescendo murmur of minute ventricular septal defect closely resembles an ejection systolic murmur The murmur is loudest at the fourth left intercostal space (*4LS*) where a striking decrescendo follows the intense high frequency murmur which reaches a crescendo in the first quarter of systole At greater amplification (*3* compared with *10*) distinct high frequency low amplitude vibrations reach the aortic component (A2) of the second sound *suggesting a regurgitant systolic murmur* despite its diamond shape The murmur is much softer in the pulmonary area and splitting of the second sound is normal

detect the intracardiac murmur according to the technique described by Lewis and associates[9] and elsewhere[1] Intracardiac and external sound tracings were simultaneously recorded with the electrocardiogram and sometimes with intra arterial and intraventricular pressure pulses and the influence of amyl nitrite and phenylephrine on these was studied[1]

Results

In all 12 patients amyl nitrite softened the early systolic murmur whereas in all 8 to whom phenylephrine was administered the murmur became much louder and longer These responses identified the murmur as a left sided regurgitant *murmur* despite its atypical shape

Of the 8 patients catheterized only one showed a questionable small rise in oxygen saturation at the right ventricular level suggesting a left to right shunt of about 10 per cent In the remainder no shunt was detectable by blood sampling techniques even after phenylephrine This confirms the limitations of this method even when adequately performed using multiple samples in rapid succession for detecting small left to right shunts[1] All patients had normal right heart and systemic pressures with no evidence of pulmonary or infundibular stenosis

In 7 patients dye dilution curves were obtained at a systemic artery after injection into the right side of the heart None of these curves revealed any evidence of a left to right shunt thus confirming the *failure of this method to detect small left to-right shunts*[13] In 6 patients phenylephrine failed to elicit any detectable shunts by this method (Fig 1) but in one patient in whom the dilution curve was

recorded from a Norman earpiece densitometer a clear-cut small left to right shunt was demonstrated only after phenylephrine

With regard to the 5 patients studied by the technique employing two venous catheters very small shunts which ranged from about 4 to 9 per cent were demonstrated in all and localized in every case to the right ventricle In one patient the shunt was so small that the curve obtained from the right ventricle was inconclusive Nevertheless a shunt was convincingly demonstrated after phenylephrine had increased the pressure gradient (Fig 1) The percentage shunt diminished with amyl nitrite and increased after phenylephrine in all patients However the magnitude of the change was slight as compared with the pronounced changes in intensity of the murmur and in simultaneously recorded pressures (Figs 1 and 4)

Of the 3 patients studied by the *phonocatheter* high frequency murmurs of crescendo decrescendo shape were recorded within the right ventricle in all These tracings had a configuration similar to that of the simultaneously recorded external tracing (Fig 2) However it was impossible to determine with any certainty whether the defect arose in the membranous or muscular septum Muscular defects are usually situated at any level in the muscular septum subjacent to the anterior ventricular wall[14] but occasionally they are found along the posterior wall and they may be multiple Hence the murmur should be picked up anteriorly and inferiorly but because of difficulty in accurately locating the phonocatheter during fluoroscopy in the anteroposterior view we achieved little success in siting the defect However in one patient the murmur was only recorded at the apex of the right ventricle which strongly suggested a very low and unusually situated defect This seemed to account for the external murmur being loudest at the mitral area

Amyl nitrite shortened and softened both the external and intraventricular murmurs whereas phenylephrine had the reverse effect (cf Fig 4 of Schrire and associates[11]) Thus established that the murmur within the right ventricle was a left sided regurgitant murmur even though it had the shape of an ejection type of systolic murmur Most patients had intrapulmonary ejection systolic murmurs[11] which is a normal finding[9 10]

Clinical features

Of the 12 patients 6 were girls and 6 were boys they ranged in age from 3 to 15 years In 4 the murmur was first discovered in early infancy In the others it was found accidentally and was the only indication of heart disease Physical development was normal in all and none had symptoms referable to the heart Associated congenital deformities were absent and anterior bulging of the sternum was not present A systolic thrill was palpable in only 2 patients Electrocardiographic and radiologic findings were completely normal in all

Auscultatory and phonocardiographic findings

The heart sounds were normal in all but at the site of maximal intensity of the murmur it was difficult to hear the first sound because the murmur commenced with it Splitting of the second heart sound was never more than 0 03 second during expiration and increased in the normal manner during inspiration Ejection sounds were absent An apical third sound presumably physiologic was heard in 2 patients it was very loud and misleading in one whose murmur was loudest at the mitral area Mid diastolic apical flow murmurs were absent in all

The *systolic murmur* was Grade 3 in intensity in 10 and Grade 2 and Grade 4 respectively in the other 2 patients (Intensity was graded from 0 to 6) The site of maximal intensity was usually sharply localized in the third or fourth intercostal space at the left of the sternal border but in one patient it was loudest at the mitral area The murmur was never widely conducted being particularly loud in a restricted zone and soft elsewhere tending to radiate toward the apical and pulmonary areas The same murmur was not heard in the vessels of the neck In one exceptional patient the murmur was loudest at the mitral area and was better conducted to the fourth left intercostal space than to the axilla The murmur had a high frequency quality in all Respiration had a variable effect in 2 patients the

murmur became much softer during inspiration, probably because of a shift of the heart away from the chest wall. In another it became more pansystolic during inspiration.

The most unusual but characteristic feature was the shortness of the murmur. Commencing immediately with the first sound, it reached a striking crescendo by the first third of systole and then softened rapidly, resulting in an early diamond-shaped murmur confined to early systole. This, together with the apparent cessation well before the aortic second sound, caused it to resemble closely an ejection systolic murmur (Fig. 3). However, the sound tracing, when recorded with increased amplification, usually provided evidence that the murmur was in fact a regurgitant type of murmur. The presence of low-amplitude, high-frequency, inaudible vibrations in the latter quarter of systole extending into the aortic second sound suggested that regurgitant flow was in fact continuing throughout systole (Fig. 3).

Response to amyl nitrite and phenylephrine

The response to amyl nitrite and phenylephrine was the most important feature in the diagnosis, since it at once excluded ejection systolic murmurs. Whereas ejection systolic murmurs intensify after amyl nitrite and change very little with phenylephrine, this murmur behaves like a left-sided regurgitant murmur.

In all 12 patients the murmur softened greatly and usually but not always shortened during the peak systemic hypotensive phase of *amyl nitrite* action (Figs. 4A and B). At this phase it lost its crescendo and seemed confined entirely to the first quarter of systole, having a rapid decrescendo after the first sound, which had been intensified by the tachycardia. Occasionally, although very soft, the murmur was more clearly pansystolic at this phase. In one patient the murmur disappeared completely. During the gradual rise in systemic pressure and deceleration of the heart rate the murmur gradually recovered and usually after 60 seconds had again developed a crescendo in early systole and a rapid diminuendo thereafter. The changes correlated extremely well with the fall and rise of left to right ventricular peak systolic pressure gradient (Fig. 4A). In 5 patients amyl nitrite was shown to diminish the minute left to right shunt (Fig. 4B); the diminution in percentage shunt volume was less striking than the change in intensity of the murmur and in pressure gradient.

In all 8 patients who were given *phenylephrine* the murmur intensified greatly and lengthened considerably, becoming pansystolic. However, the shape of the murmur remained crescendo-decrescendo (Figs. 1, 5, and 8) except during premature systoles and after short preceding diastoles in sinus arrhythmia (Fig. 5). The intensification of the murmur was shown to correlate well with the increased ventricular pressure gradient (Figs. 1 and 5). Since phenylephrine elevated the systemic pressure greatly and the pulmonary arterial pressure only slightly, the gradient across the defect was always considerably elevated.[13] The fall in cardiac output[13] had no influence on intensification of the murmur.

Apparent spontaneous cure of small ventricular septal defect

Two patients, aged 4 and 8 years, who had loud short crescendo-decrescendo systolic murmurs which became much softer after amyl nitrite were of extreme interest in that their murmurs spontaneously disappeared during follow-up (Fig. 6). Although the diagnosis of ventricular septal defect was not proved, the site of the murmur, its shape, quality, and behavior with amyl nitrite was sufficient to create strong suspicion of a very small ventricular septal defect. Moreover, in the light of facts now gained from the proved cases, the defects must have been very small, possibly in the muscular septum and therefore capable of spontaneous closure during physiologic growth of the heart and septum.

Differential diagnosis

The differential diagnosis is that of a short crescendo-decrescendo systolic murmur unaccompanied by abnormal clinical, electrocardiographic, or radiologic signs. Clearly, the short ejection systolic murmur of large ventricular septal defect with equal

ventricular pressures and elevated pulmonary resistance does not enter the discussion because of the grossly abnormal associated findings.

The murmur under consideration may suggest mild pulmonary or infundibular stenosis, mild aortic or subaortic stenosis, innocent parasternal murmurs of childhood, and pulmonary ejection murmurs due to increased flow or unknown factors. To this list should now be added a minute ventricular septal defect. Whereas a small defect of the Roger type with its classic loud pansystolic murmur is one of the easiest to diagnose, it is now apparent that a small defect cannot be excluded when a murmur is not pansystolic. Once this possibility is suspected, the use of amyl nitrite and/or phenylephrine should quickly confirm or disprove the diagnosis at the bedside (Figs. 7 and 8). Phonocardiography is not essential but may show some finer points of differentiation from ejection systolic murmurs.

Differentiation from mitral incompetence is usually easily made by the site and radiation of the murmur, although the murmurs respond similarly to amyl nitrite and phenylephrine. However, the distinction may not always be easy, as shown in one of our patients (Case 6, J. T., Fig. 8). The short systolic murmur in this girl was loudest at the mitral area, accompanied by a loud third heart sound and a slightly overactive left ventricle. Mitral incompetence seemed much more likely, but the history of a murmur from infancy, the crescendo-decrescendo shape of the high-frequency murmur, and absence of a history of rheumatic fever or features of corrected transposition led us to suspect a minute septal defect; this was confirmed. The possibility, therefore, of a low minute septal defect must be considered when an apical systolic murmur exhibits an early crescendo-decrescendo pattern. Such a shape must be unusual for mild mitral incompetence, in which condition the murmur is either decrescendo, plateau, or has a late systolic crescendo.

Tricuspid valvular incompetence would seldom require consideration. Intensification of the murmur after inspiration and amyl nitrite[4] is an additional distinctive feature.

Discussion

The mechanism of the short crescendo-decrescendo murmur of these minute septal defects is intriguing. In shape and duration this murmur is entirely different from the classic pansystolic murmur of small ventricular septal defect, which murmur extends from the first sound to beyond the aortic second sound, having either a rectangular shape denoting constant intensity or a late systolic crescendo. Yet both murmurs behave similarly after amyl nitrite and phenylephrine, thus proving that both are dependent on the pressure gradient between the left and right ventricles. Why then the difference in configuration? The murmur of a small septal defect is typically pansystolic because shunt flow is maintained throughout systole by the large pressure differential between the two ventricles, continuing from the isometric contraction phase into the isometric relaxation phase. The plateau or rectangular configuration also implies that the defect remains patent throughout systole, although we suspect that partial occlusion of the defect during late systole may account for the striking late crescendo often encountered in small septal defects. A logical deduction is that the atypical short crescendo-decrescendo murmur is due to occlusion or narrowing of the small defect during early systole. The murmur commences in the usual fashion with the first sound, but instead of maintaining a plateau shape it intensifies very rapidly, suggesting increasing velocity of jet flow. The peak of the crescendo is reached by the first third of systole, which probably reflects the moment of critical narrowing of the orifice, beyond which the available pressure gradient is insufficient to maintain jet flow and velocity. Thereafter, the defect is presumably progressively diminished in size, accounting for the rapid decrescendo of the murmur and its frequent cessation before the aortic second sound.

We have further indirect evidence to support the view that complete or nearly complete closure of the small septal defect during systole accounts for the atypical murmur.

1. When the left-to-right ventricular pressure gradient is greatly increased by phenylephrine, the murmur intensifies.

Y SMALL VSD

100 BA

PA

0 1 2 1 2 1 2 1 2

3LS SM SM

A P A P

PA

BEFORE DURING 20" AN INHALATION AFTER 10 20" 30 1' 1'15"

Fig. 41. Case 1, T. V. Brachial and pulmonary arterial pressure tracings synchronously recorded with sound tracings. Note the wide peak systolic pressure gradient and the short crescendo-decrescendo systolic murmur. During the 20 seconds of inhalation of amyl nitrite the systemic pressure falls steeply and the pulse contour changes strikingly, whereas the pulmonary pressure falls gradually. The resultant gross reduction in ventricular pressure differential causes great shortening and softening of the systolic murmur. By 1 minute and 15 seconds the gradient and murmur have almost recovered. The response is that of left-sided regurgitant systolic murmur.

100

50

AMYL NITRITE INHALED 38 sec

DYE INTO DISTAL PA

10 SEC

INJECTION INTO DISTAL PULM ART

SAMPLING FROM MAIN PULM ART

CONTROL

AFTER AMYL NITRITE

[VERY SMALL VSD]

Fig. 1B Case 1. Before amyl nitrite there is a very small left to right shunt of about 7 per cent when the systemic pressure is 150/100 mm Hg. The dilution curve during the peak response to amyl nitrite (blood pressure of *100/50* mm Hg) (*arrow*) shows reduction in the left to right shunt accounting for the reduction in murmur after amyl nitrite.

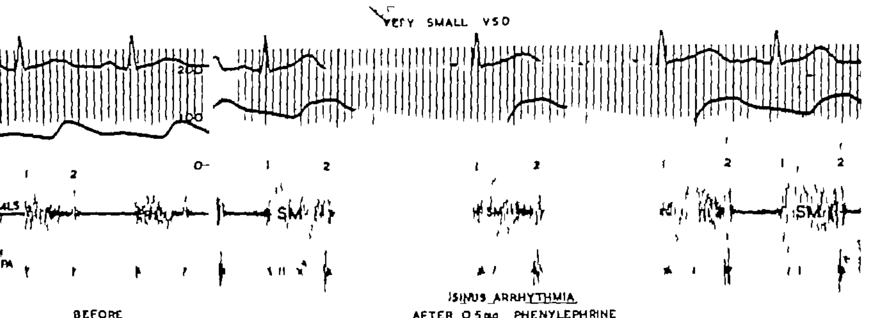


Fig. 5. Case 8, C.M. This figure illustrates two features. The great intensification of the murmur after phenylephrine proves that the murmur which has the appearance of an ejection murmur is a left-sided regurgitant murmur. Marked sinus arrhythmia develops during which there is little change in systemic pressure but striking and paradoxical change in the length of the murmur and in its intensity in the last quarter of systole. After the short diastole the murmur is longer and louder in end-systole, whereas after the long diastole the murmur has a quicker decrescendo, ending before the second sound (see text).

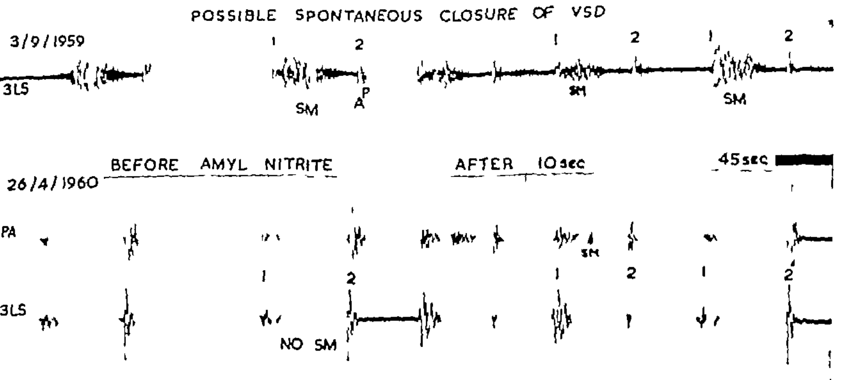


Fig 6 Case 11 M.L. Possible spontaneous cure of ventricular septal defect. On Sept. 3 1959 a localized early systolic diamond shaped murmur was recorded at the third left sternal border (3LS). After amyl nitrite the murmur softened considerably, suggesting a typical very small ventricular septal defect. On April 26 1960 the murmur had completely disappeared; no murmur was recordable. After amyl nitrite a soft physiologic ejection murmur emerged at the pulmonary area. The disappearance of the murmur suggested spontaneous cure of small ventricular septal defect.

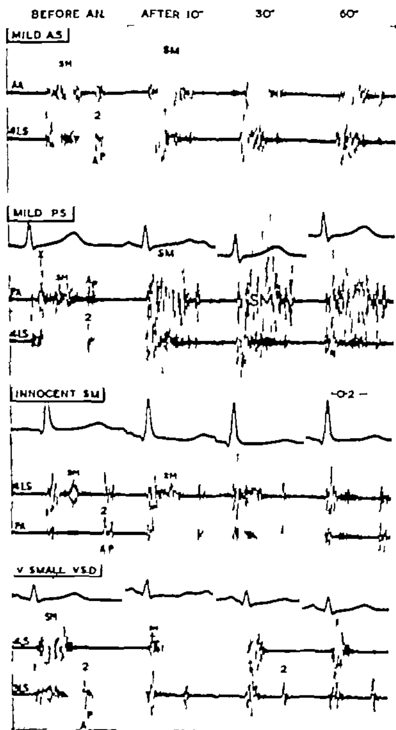


Fig. 7. The value of amyl nitrite in the differentiation of various ejection systolic murmurs associated with normal electrocardiographic and radiologic findings from the typical murmur of very small ventricular septal defect (Case 4, L.D.). All ejection murmurs intensify, especially those due to mild aortic and pulmonary stenosis. The innocent musical parasternal murmur intensifies slightly, suggesting a nonstenotic ejection mechanism. By contrast, the diamond-shaped murmur of minute ventricular septal defect softens and shortens strikingly during the peak response to amyl nitrite, and even at 60 seconds the systolic murmur (*SM*) has not recovered.

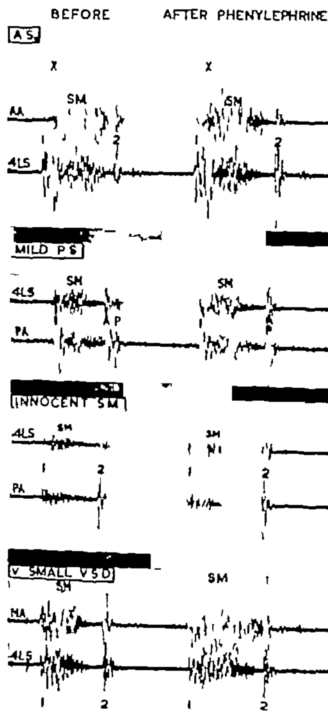


Fig 8 Value of phenylephrine in the differentiation of ejection systolic murmurs with normal ECG and radiological findings from murmur of minute ventricular septal defect (Case 6 L T) Before phenylephrine there is close resemblance in shape and duration between all the murmurs but afterward the ejection murmurs change insignificantly whereas the diamond shaped ventricular septal defect murmur intensifies and lengthens greatly thereby proving a left sided regurgitant murmur Although the murmur was maximal at the mitral area this patient was thought to have a low minute ventricular septal defect in the muscular septum (see text) Note preservation of diamond shape despite pronounced response to phenylephrine during which the systemic blood pressure rose from 110/50 to 160/90 and pulmonary arterial pressure from 25/8 to 34/18 mm Hg

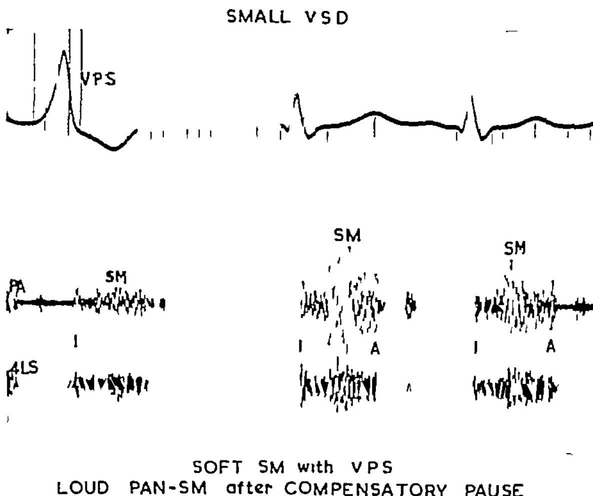


Fig 9 The usual response of the murmur to arrhythmia in small ventricular septal defect with classic pansystolic murmur The murmur remains pansystolic throughout with no significant change in shape but is softer with the premature systole and slightly louder after the compensatory pause (compare with Fig 10)

lengthens reaching the aortic second sound this proves that the defect is in fact patent throughout systole However despite these pronounced changes the crescendo-decrescendo shape is maintained suggesting that the defect does shut down considerably (Figs 1 5 and 8) This behavior *is quite unlike that of a small* ventricular septal defect with a pansystolic murmur in which situation the entire murmur and especially the latter half blow up after phenylephrine

2 The behavior of the systolic murmur during various arrhythmias is paradoxical During premature systoles provided they are not extremely premature and after the compensatory pause the classic pansystolic murmur of a small ventricular septal defect remains pansystolic despite being softer with the premature systole and louder after the pause (personal observations) (Fig 9) However in 3 patients with the atypical murmur a paradoxical response resulted from the arrhythmia The most striking example is shown in Fig 10 During the premature systole the murmur *lost its crescendo and lengthened* becoming a typical plateau or rectangular systolic murmur However after the compensatory pause the murmur reverted to its former shape being then even shorter than before Even though very *loud* the crescendo and abrupt decrescendo occurred in very early systole suggesting premature and more complete occlusion of the defect The same paradoxical behavior was observed in 2 patients with sinus arrhythmia (Fig 5) suggesting that the alteration in

the shape of the murmur is not dependent on ectopic beats but rather on the changing heart rate. A possible explanation for these observations is that after the short diastole which resulted in less initial diastolic stretch and consequent less vigorous ventricular (and septal) contraction, the small defect remained patent throughout systole, thus accounting for the pansystolic murmur. However, after the lengthened diastole of the compensatory pause, ventricular contraction would be more vigorous and possibly result in premature and more complete occlusion of the defect, reflected by the very short murmur. In another patient whose minute defect was thought to be low in the muscular septum, nodal rhythm with ventricular aberration developed for three systoles during the peak response to phenylephrine. Despite the great intensification and lengthening of murmur induced by phenylephrine, the murmur almost disappeared during the three systoles with aberrant ventricular conduction. When ventricular conduction returned to normal, the murmur immediately recovered in intensity. Since the heart rate and systemic pressure remained virtually unchanged, the dramatic softening of the murmur was attributed to early systolic closure of the defect by an altered mode of spread of septal contraction caused by the aberrant ventricular activation.

3 During the height of the tachycardia produced by amyl nitrite, when the murmur was maximally softened, it was paradoxically lengthened in 4 patients, with vibrations reaching the aortic second sound. However, during deceleration the murmur shortened whereas the intensity in very

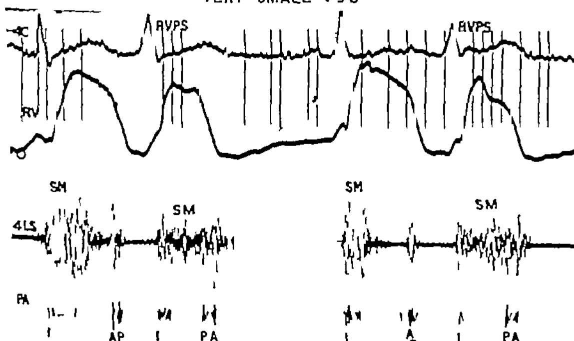


Fig 10 Case 8 C M Paradoxical response of murmur to arrhythmia in minute ventricular septal defect. The murmur in the first systole is diamond shaped with striking crescendo and decrescendo of high frequency vibrations. With the right ventricular premature systole the murmur becomes a plateau pansystolic murmur with no mid-systolic crescendo and vibration of lower frequency. Right ventricular pressure is only slightly reduced and there is reversed splitting of the second sound with the murmur continuing beyond A_2. After the compensatory pause the right ventricular pressure rises only slightly, but the murmur changes strikingly, resuming its former shape and very high frequency; however, the crescendo is even earlier and the decrescendo much more abbreviated. The murmur again becomes plateau pansystolic with the next premature (see text)

early systole returned. The crescendo-decrescendo shape was usually restored on return of the heart rate to the normal level, usually after 1 minute. These observations suggest that during the phase of pronounced tachycardia the defect was less effectively occluded in mid-systole, permitting pansystolic flow despite the reduced left ventricular pressure.

Although this evidence strongly supports the idea of a fluctuating size of the orifice in the determination of the shape of the murmur, it does not necessarily imply that the defect is in the muscular ventricular septum, tempting though such an assumption may be. Unfortunately, the site of the defect in the septum could not be determined accurately in this study, since cineangiographic apparatus was not available. In only one patient was there strong clinical and phonocatheter evidence of a low defect in the muscular septum. Although it would appear that a defect in the muscular septum is more apt to become smaller during contraction of the ventricular septum than a defect in the membranous septum, there is some evidence that membranous defects, too, may be squeezed closed by contraction of hypertrophied muscle of the septum and crista supraventricularis. Alternatively, the defect may be occluded by the septal leaflet of the tricuspid valve. Even though we believe that the former possibility is unlikely in our patients in view of their normal dynamics, absence of intraventricular pressure gradient, and triviality of shunt, these arguments do not exclude the possibility of a small membranous defect becoming occluded by the tricuspid valve. Even the strongly suggestive evidence of spontaneous cure of 2 of our patients does not prove the existence of a muscular septal defect. Cineangiocardiography, observations at operation, or necropsy may provide the ultimate proof.

The recognition of small and minute ventricular septal defects is important for several reasons. It is well established that the natural history and prognosis of ventricular septal defect depends on the size of the defect.[3] The rarity of encountering ventricular septal defect in persons over 40 years of age has been claimed to support the ultimate poor prognosis.[29] However, it is difficult to believe that small defects in persons with normal dynamics shorten life, and we wonder whether the rarity of ventricular septal defect in adults may partly result from the spontaneous closure of small defects, especially those in the muscular septum. In support of this is our experience with 2 patients who lost their murmurs during follow-up. The possibility of spontaneous disappearance of septal defect was discussed by French,[1] Stamm,[2] and Parkes Weber[3] in 1918 and by others[4,5] since. Possibly, some of the so-called innocent parasternal murmurs of childhood which have been reported to disappear[6] may have been small septal defects undergoing spontaneous cure.

The true incidence of small defects in the muscular septum is unknown. Patients seldom die from them. They are readily missed at routine necropsy and even at ventriculotomy for large membranous septal defect because they are buried in between the trabeculae carneae. The fairly frequent finding of muscular septal defects, sometimes multiple, at the time of operation for membranous septal defects[14] suggests that the reported incidence of muscular defects is too low. When the defect is very small and unassociated with abnormal symptoms and signs, the murmur may be considered to be innocent. If septal defect is suspected, catheterization may either not be considered justified or, if performed, fail to reveal a shunt. We suspect that the incidence of such defects is considerably higher than hitherto stated, but that many of the small defects may close spontaneously with the growth of the heart. We hope that more information about the incidence and natural history will be forthcoming now that the diagnosis of small and minute defects is possible.

Summary

1. A study has been made of 12 patients with atypical systolic murmurs that were believed to be characteristic of minute ventricular septal defects. In 7, left-to-right shunts of under 10 per cent were demonstrated at the ventricular level by refined techniques.

2. Unlike the pansystolic murmur of a small ventricular septal defect, the murmur of a minute defect is confined to early

systole and has a crescendo-decrescendo configuration which simulates an ejection systolic murmur

3 Since there are no accompanying clinical electrocardiographic or radiologic abnormalities in these patients the atypical murmurs are apt to be confused with left sided or right sided ejection systolic murmurs whether innocent or due to mild stenosis However the response to amyl nitrite and phenylephrine readily identifies the atypical septal defect murmur as a left sided regurgitant murmur

4 Simple auscultation and phonocardiography using amyl nitrite and/or phenylephrine proved superior in diagnosis to conventional methods of cardiac catheterization in the diagnosis of minute septal defects

5 Routine methods of cardiac catheterization and systemic arterial dye-dilution techniques failed to demonstrate such diminutive shunts However the technique which employs two venous catheters for obtaining dye dilution curves from the right heart and intracardiac phonocardiography successfully established the diagnosis The methods and use of vasoactive drugs to manipulate the shunt are discussed

6 The mechanism of the crescendo decrescendo shape of the murmur is believed to be partial occlusion of the small defect in early systole during contraction of the ventricle and septum The reasons for this belief are fully discussed

7 The site of the defect in the ventricular septum could not be established although in one patient there was good evidence of a defect in the low muscular septum

8 In 2 patients the murmur disappeared during follow up suggesting spontaneous closure of the defect

9 Now that the diagnosis of very small septal defects with atypical systolic murmurs is possible more light should be thrown on their incidence and natural history

Addendum

After this paper had been submitted for publication an important paper was published by Evans and associates[14] showing that spontaneous closure is not uncommon in small septal defects and may rarely occur with lesions large enough to present initially with congestive cardiac failure The authors confirm that a short early high frequency systolic murmur indicates a very small septal defect and have observed loud pansystolic murmurs in infancy becoming shorter and softer before ultimately disappearing By comparing catheterization data in 5 patients with sound tracings they showed that softening and shortening of the murmur was associated with decreasing magnitude of left to right shunt That disappearance of the murmur indicated disappearance of the shunt was established by recatheterization in 2 patients

The authors also believe that defects giving these characteristics are likely to be located in the muscular septum In one subject a selective cineangiocardiogram from the left ventricle demonstrated a small defect in the lower interventricular septum and in 2 additional patient intracardiac sound tracings revealed a short early systolic murmur localized to the apical region of the right ventricle suggesting a muscular septal defect

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t return l Th crese low ... wed hi, w u ll re t red on urn of th heart r te t the r ...mal level u ..ally fter l m ut These 'hservat ns ... es th dur n the ph ... f prom unced t h r' the efect w les effectively ...'ul ed in m les ol permitting p ... les tc the reduced left ven ...r' r p es are

Alth ... h th evil nce r ... ly upport ... l t of a fluctuati ... r ... f the orifice th d term n tion cf the h ... f th murmur it d es n necess rily im ly th t the d fec ... is in th muscular entricular septum tem, ti n th ... h a h n ump tion ma be Un rtun el the ... e of th defect in the sep um co ll n ... be de term ed ccurately in th ... tud ... e ... cin ... gi aph ... pro tu ... r ... vail ... l!' In onl one p tient ... r ... there ... ma cl n d nd pl ... mor the er evi ence f a l ... defect n th muscular septum Althou h it w ... ll p ... ear th t a d fect in the muscular sep tum i more p ... t t become mall r durin c ntraction of th ventricu lar septum than d fect in the membranous se tum there some evidenc that mem br n ... u defect ... t ... r m ... l squeezed closed b contr ction of h pertrophied muscle of the septum an l ... ertai upra entr cular. Alternativel the defect may be ... ccl ... d b the sep tal leaflet of the tricu p l al e Even th u h we believe that th ... form r possibility is unlikely in our patient in view of their n rmal d namics absence f intraventricul r pres ure gradient and trivialit ... cf hunt these argument do not exclude the pos ibil ty of a mall membran us defect becoming oc cluded b the tricu d valve Even the stron ly ... gestive evidence of pontaneous cure of 2 of our patients does not prove the exi tence of a muscular septal defect Cine angiocardiographic observations at opera tion or necropsy may provi le the ultimate proof

The recognition of small and minute ventricular septal defects is important for several reasons It is well establi hed that the natural hi tory and prognosis of ven tricular sep al d fect depends on the size of the defect.[1] [4] The rarity of encountering ventricular septal defect in persons over 40 years of age has been claimed to upport the ultimate poor progno s ... However it is d ff ult t ... l ... s that mall defects in p rsons with norm l dynamics "shorten l" ... n l we won ler whether the rarity of ventricular se al defect in a lult may partly result from the ... ont neou clos re cf mall l fect es ecially th se in the muscular sep um In supp rt of this is our experien e with 2 patient wh l ... s the murmurs during f llow up The pos bil t ... f ... pont n ... u ... d sapp ara ce of sept l l fect wa d scu sed by French ... St umm ... n l l ... rkes Weber[3] in 1918 and b ... l ... n ... ince ... l ... s ... ll ... s ... me cf the so-called in nocent par ... temal murmurs cf ch ldhoo l wh h have been reported to lisappear ma ... have been small septal defect ... un ler ... go ... n ... pontaneous cu e

The true incidence cf small d fect in th muscul r se tum i ... unknown l at t sel lom die from them The ... are rea lily m sed at routi e necr ... s ... ar l even at ventriculo ... om ... f ... r large membranou sep tal defect because th ... are l ... ed ... n l ... tween th ... trabeculae carneae Th ... fairly frequent f ... nd ... of muscul r sep al d fects sometimes multi le at th time of o era tion for membranou ... sept l defects ... ... gest that the reported incidence of muscu lar defect ... t ... o l ... w When the defect i very m ll and una sociated with abn rmal symptom nd ... n the murmur may be con lered to be innocent ... if sep tal defect is su ected catheterization ma either not l ... con dered ju tified or if performed f il to reveal a hunt We su pect that the inci lence of uch defect is con id erall ... higher than hitherto ... ated but that many of the mall defects may close pont neou ly with the growth of the heart We h ... pe that more information about the incidence and natural hi tory will be forth coming n ... w that the diagnos ... of mall and minute defects is pos ible

Summary

1 A study has been made of 12 patient with atypical systolic murmurs that were believed t be characteristic of minute ventricular septal defect In 7 left to-right hunts of un ler 10 per cent were demon strated at the ventricular level by refined techniques

2 Unlike the pansystolic murmur of a small ventricular septal defect the murmur of a minute defect is confined to early

Case reports

Corrected transposition of the great vessels
Report of 2 cases

H S Badawi M D
M K Badr M D
Y A Habib M D
B Jonsson M D
A Khadr M D
H Khalil M D
I Taufick M D
Alexandria Egypt

In corrected transposition of the great vessels the aorta is situated anteriorly and usually to the left and the pulmonary artery posteriorly and usually to the right The route of blood flow however is normal The correction occurs by inversion in different regions bulbar sinoatrial or ventricular[2] The venous blood of the systemic veins enters the right atrium and passes through the bicuspid atrioventricular valve to enter a ventricle with the structural appearance of a left ventricle from which the pulmonary artery takes off The arterial blood of the pulmonary veins enters the left atrium and passes through a tricuspid atrioventricular valve to enter a ventricle with the structural appearance of a right ventricle from which the aorta takes off There is inversion of the coronary arteries

The malformation is rarely isolated In most cases there are septal defects or valvular lesions Incompetence of the atrioventricular valve on the arterial side (mitral incompetence) has been reported[4] Various grades of atrioventricular block are a common feature As in many other congenital heart malformations the condition was first recognized at post mortem When the clinical picture was described the antemortem diagnosis became possible The clinical findings vary to a great extent however depending on the type of associated lesions

Within a period of one month we met with two cases diagnosed clinically

Case reports

Case 1 The physical and mental development of this 7-year-old boy had been normal Since infancy he had suffered from dyspnea on exertion but had never been cyanotic A systolic murmur was first detected when he was 4 years old Examination of the cardiovascular system showed heart rate of 56 beats per minute The blood pressure was 130/75 mm Hg in the upper and lower limb There was no precordial bulge The apex beat was heaving and located in the fifth intercostal space at the midclavicular line There was a palpable second sound over the pulmonary area Auscultation revealed marked accentuation of the second sound which was not split and had its maximal intensity over the second left intercostal space The first sound was changing in intensity A Grade 4 early systolic murmur was heard over the base as intense to the right as to the left of the sternum A longer

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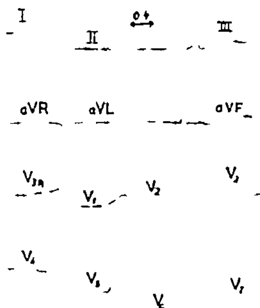


Fig 1 ECG Case 1 N t complet AV block deep Q in Le l III I V deep S in V nd light depres of S-T V

t le murmu f the same inten ty ud l le ov the pex nd t ansmitted t the l ft ill nd t the back There w lso sl rt low frequency m ldiastolic murmur

The ECG (Fig 1) showed complet AV block deep Q Lead III nd V deep S in I I V nd light depres on of S-T in Le d V

ROENTGENOLOGIC EXAMINATION The roentgenogram (Fig) showed markedly enlarged heart th pturned pe nd n bnormally straight line in the upper left border The ortic rch had normal po t t the left In the l t ral iew the he rt had n ncre sed surf of contact with the terior hest wall nd the left trium w slightly d l ted Th central lung essel re somewh t wid ned

HEART C THETERIZATION C theteriz t on d t are gi en i Table I The catheter introduced t left cubit l ei pa sed from the en ous entricle out into the pulmonary rtery in more med al and posterior position than norm ll (Fig 3) There were no left to-right hunt The systolic pres ure in the pulmon ry rtery w ncre sed with large pulse mpl tude and only light increase in the mean pressure A systolic pressure gradient of 19 mm Hg was found acro the pulmonary al e In the pre ence of complete AV block the expected increase in the stroke olume can expl n this pressure gradie t without y t mic steno is The pulmon ry arterial wedged pres ure wa not increased but the w es were abnormally high and showed a rapid f ll (Fig 4)

Case 2 The ph sical and mental development of this 5½ year old girl had been normal She had had no heart symptoms but was admitted to the hospital because of enlarged breasts a condition which had its onset 8 months prior to hospitalization

At r tine ex mination a murmur d scovered Phy ical ex mi t rev led the gl l lar hyper trophy f the l t The heart r t during sleep 9 l t p mi t The bl l pres ure 105/65 the pper l mb 110/65 mm H in the l er l mbs Ther w n precordial bul The pex be t w normal The sec l h und palpable over the p lm ry area On auscultation there marked ac entuat f the second he nd b h not pl t nd h l it ma m l ten ty the sec l l ft i tercostal pa There l ude l y t le m rmur f l ther h h f quency wh h en led lef the sec l ur l which f ma mal nt ty over the m ll e f th tern m at the le l f th th rd interc t l pace On ph ne rd r phy the murmur fou l t be d mo l sh ped

The ECG (Fig 5) sl owed ormal s n rhythm with l hthy prol nged P Q time (0 20 secon l) l l p Q in Le l III l V

ROENTGENOLOGIC EXAMINATION Th roentgenogram (Fig 6) showed rather norm l s zed h art



Fig Case 1 Enlargement of the heart upturned pex abnormally straight pper l ft border and slightly dilated left atrium



Fig 3 Case 1 The catheter introduced from the left arm pa es through the rught trium nd enous entricle int the pulmonary artery which has a medial position

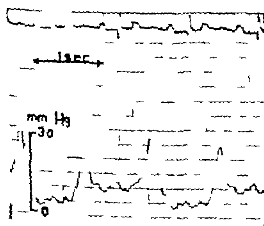


Fig 4 Case 1 Pulmonary arterial wedged pres ure Note the high waves

but one that was abnormal in configuration The apex was ptturned and the left upper border was abnormally straight The great ssels were not seen at their usual sits on the left of the mediastinum There was right aortic arch and the descending aorta passed to the right In the lateral view the heart bowed a increased surface of contact against the anterior chest wall The left trium was not enlarged The ascularity of the lungs was normal

HEART CATHETERIZATION Catheterization was performed from the saphenous ein When the catheter passed from the enous entricle out into the pulmonary artery its position was more medial and posterior than occurs normally (Fig 7) There was pressure gradient across the pulmonary al of 21 mm Hg A left to-right shunt was present The pulmonary wedged and the pulmonary arterial pressures were normal (see Table 1)

ANGIOCARDIOGRAPHY No film hanger was d ble Twenty milliliters of 0 per cent Urographine was injected by hand through the catheter placed in the enous entricle nd few exposures were made within 8 seconds The pulmonary artery was found t be placed to the ri ht of the scending aorta (Fig 8)

Discussion

In both of these cases a presumptive diagnosis w s made with the aid of physical findings ECG and roentgenologic examina tion The diagnosis w s confirmed by heart catheterization A markedl accentuated single second sound over the pulmonary area in conjunction with n electrocardio gram and roentgenologic picture which excluded pulmonary hypertension of a high degree was a characteristic feature The roentgenologic examination gave also some positive evidence of transposition of the gre t essels by absence of the pulmonary artery shadow at its normal ite The transposition must ha e been corrected because no cyanosis was present The heart catheterization was decisi e for the diagnosis since the position of the pulmonary artery was established by passage of the catheter from the enous ventricle into the pulmonary artery Furthermore the results of heart catheterization were im portant for the diagnosis of the associated lesions

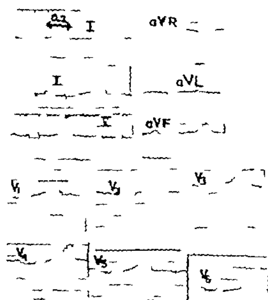


Fig 5 ECG in Case 2 Note lightly prolonged P Q time and deep Q in Leads III and aVF

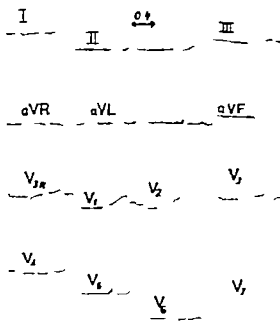


Fig. 1. ECG in Case 1. Note complet A V block, deep Q in Lead III and V, deep S in V and light depres of S-T in V

ys tolic murmur of the same inten ity audible over the pex and was tran mitted to the left axilla and t the back. There as also hort low frequency mid-dia tolic murmur

The ECG (Fig. 1) howed complet A V block, deep Q in Lead III and V, a deep S in Lead V and l ght depre ion of S-T in Lead V.

R ENTGEN LOGIC EXAMINATION. The roentgenogram (Fig. 2) showed markedly enlarged heart with an pturned pex and an bnormall traight line in th upper lef border. The aortic arch had normal posit n to the left. I the lateral iew the heart had an increased surface of contact with the anterior chest wall and the left trium was slightly dilated. The central lung essels were somewhat widened.

HEART CATHETERIZATION. Catheterization data are given in Table I. The catheter introduced int left cubital em, pa sed from the enous ventricle out into the pulmonary artery in a more medial and posterior position than normall (Fig. 3). There were no left-to-right shunt. The st le pressure in the pulmonary artery was increased with a large pulse mplitude and only a light increase in the mean pressure. A systolic pressure gradient of 19 mm. Hg was found acros the pulmonary valve. I the presence of comp ete A V block, the expected increase in the stroke olume can explain this pressure gradient without any anatomic tenosis. The pulmonary arterial wedged pressure was not increased but the v waves were abnormally high and howed a rapid fall (Fig. 4).

Case 2. The phy ical and mental development of this 5½-year-old girl had been normal. She had had no heart symptoms, but was admitted to the hospital because of enlarged breasts a condition which had its onset 8 months prior to hospitalization. At routine examination a murmur was d scovered. I hy ical examination revealed true glandular hypertrophy of the breast. The heart rat d ring sleep w 9 beat per minut. The bl od pres ure was 105/65 in the pper l mbs and 120/65 mm. Hg in the lower limbs. There w no precordial bulge. Th pex beat was normal. The second sound palpable over the pulm nary area. On auscultation there w marked accentuation of the second sound which was not split nd had t maximal inten ity in the second l ft interco tal pace. There was Grade 4 olic murmur of rather h h frequency which ended before the second sound and which w of max mal inten t over th middle of the ternum t the level of the third interco tal pace. On phonocardiography the murmur as found t be diamond haped.

The ECG (Fig. 5) showed normal inus rhythm with a l htl prol nged P-Q time (0.20 second) nd deep Q in Lead III and V

ROENTGENOLOGIC EXAMINATI N. The roentgenogram (Fig. 6) showed a rather normal-sized heart



Fig. 2. Case 1. Enlargement of the heart upturned pex, abnormally straight upper left border and slightly dilated left atrium.



Fig 3 Case 1 The catheter introduced from the left arm passes through the right trium and enous entricle into the pulmonary artery which has a medial position

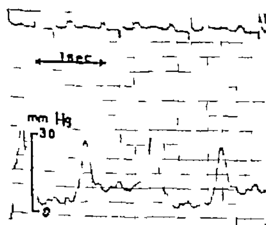


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Discussion

In both of these cases a presumptive diagnosis was made with the aid of physical findings ECG and roentgenologic examination The diagnosis was confirmed by heart catheterization A markedly accentuated single second sound over the pulmonary area in conjunction with an electrocardiogram and roentgenologic picture which excluded pulmonary hypertension of a high degree was a characteristic feature The roentgenologic examination gave also some positive evidence of transposition of the great vessels by absence of the pulmonary artery shadow at its normal site The transposition must have been corrected because no cyanosis was present The heart catheterization was decisive for the diagnosis since the position of the pulmonary artery was established by passage of the catheter from the venous ventricle into the pulmonary artery Furthermore the results of heart catheterization were important for the diagnosis of the associated lesions

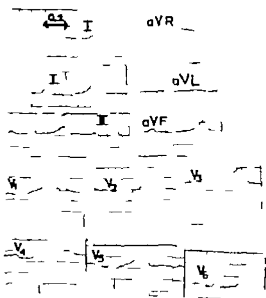


Fig 5 ECG in Case 2 Note slightly prolonged P Q time and deep Q in Leads III and aV



Fig. 6 Case. Note the pointed apex straight left upper border of the heart and right aortic arch

Because of the altered position of the great vessels and the ventricles the physical findings caused by the associated lesions are often atypical. The systolic murmur of pulmonary stenosis or atrial septal defect will have an altered position and intensity as a result of displacement of the pulmonary orifice posteriorly to the right and somewhat caudally. In Case 1 it was not possible to ascertain by means of physical examination alone what associated lesions were present. Since there was complete atrioventricular block the systolic murmur could have been due at least partially to the large stroke volume. The intensity of the murmur however was as marked over the apex and in the left axilla as over the roots of the great vessels. Furthermore the *mid-diastolic low frequency apical murmur* was so intense that it would indicate an increased diastolic filling of the ventricle (left or right) larger than that in a case of atrioventricular block. The x ray film



Fig. 7 Case. The catheter introduced from the right saphenous vein passes through the right atrium and venous ventricle into the pulmonary artery which has a medial position.

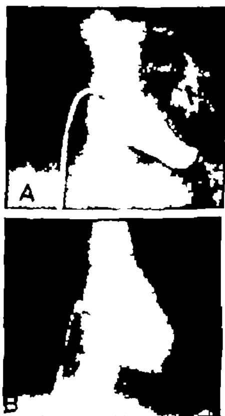


Fig. 8 Case 2. Angiocardiograph with injection of contrast medium into the venous ventricle. In A the venous ventricle and the pulmonary artery are filled and in B the arterial ventricle and the aorta are filled. The ascending aorta is situated to the left of the trunk of the pulmonary artery.

Table I Results of heart catheterization

	Oxygen content (volume per cent)				Pressures (mm Hg)			
	S V C	Right atrium	Venous ventricle	Pulmonary artery	Right atrium	Venous ventricle	Pulmonary artery	P C V
Case 1	11 5	11 3	11 2	11 3	4	68	49/9	Mean 10 wave 27
Case 2	13 1	—	13 4	13 4	2	50 2	21/7	Mean 10

Gas analysis by the Van Slyke method Pressures recorded by electromanometer (Elema)

showed a slightly enlarged left atrium probably more enlarged than the other chambers and the lung vessels were somewhat dilated Therefore incompetence of the atrioventricular valve on the arterial side or an atrial septal defect was suspected By heart catheterization it was established that no atrial septal defect was present and the shape of the pulmonary arterial wedged pressure curve indicated an incompetence of the atrioventricular valve

In Case 2 the systolic murmur was short early systolic and diamond shaped It could be explained by a mild pulmonary stenosis or a large atrial septal defect The roentgenologic examination however did not indicate an atrial septal defect The localization of the murmur was more medial than the normal pulmonary area and corresponded to the position of the pulmonary orifice in corrected transposition At heart catheterization pulmonary stenosis of a mild degree was found

Grant and associates found the second sound to be split over the second right intercostal space but single and loud to the left of the sternum in a case of corrected transposition of the great vessels associated with a probable mitral insufficiency In our cases it was not possible to hear or record the pulmonary component of the second sound which can be explained by the dorsal position of the pulmonary orifice and a very low diastolic pressure in the pulmonary artery

In many of the rather few cases with a report of the clinical findings there was an atrioventricular block In one of our two cases there was a complete and in the other a Grade I atrioventricular block

Otherwise variations in the ECG depend on the position of the ventricles and the associated malformations giving rise to ventricular hypertrophy or dilatation We did not find a reversal of the QRS pattern as has been described in some cases In both of our cases there was a deep Q in Leads III and aVF which has also been a finding in most cases reported earlier [3, 8] This pattern may be an important feature

The recognition of corrected transposition has a practical importance in cases in which intracardiac operation is contemplated because the abnormal position of the coronary arteries can interfere with a proper incision through the ventricular wall Therefore the anatomy of the coronary arteries should be outlined by the aid of angiocardiography before operation

Summary

Two cases of corrected transposition of the great vessels have been reported one with an associated mitral incompetence and a complete atrioventricular block and one with mild pulmonary stenosis and Grade I atrioventricular block In both cases proper evaluation of the physical findings ECG and roentgenologic appearance enabled us to reach the diagnosis which was confirmed by heart catheterization

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Longevity in tetralogy and trilogy of Fallot
Discussion of cases in patients surviving 40 years and presentation of two further cases

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Auckland New Zealand

With the successful development of surgical techniques for the relief or correction of congenital heart lesions interest in the natural history of these defects was heightened The advances in cardiac surgery have followed so closely on the development of accurate investigatory techniques that the clinical course of many congenital heart defects seems likely to remain imperfectly understood Rosenthal[29] has suggested that clinical material accumulating from geriatric units might reveal a greater number of older patients with congenital cardiac malformations than was formerly appreciated

In this paper the cases of two patients with cyanotic congenital heart disease are presented both of the patients died in a geriatric unit One patient with the tetralogy of Fallot appears to be the oldest woman (69 years) whose case has been recorded so far The other case is that of a woman with the trilogy of Fallot who lived to the age of 71 years

Trilogy of Fallot

Pulmonary stenosis with intact ventricular septum was at first thought to be a rare congenital heart defect In Abbott s 1936 series of 1 000 cases of congenital heart disease only 9 of the patients presented this lesion Subsequent investigators however have found this early impression to be misleading Wood in 1950 found 24 cases of pulmonary stenosis with intact ventricular septum in 200 cases of congenital heart disease an incidence of 12 per cent Geraci and associates[3] reported 6 cases of congenital pulmonary stenosis among 300 necropsy specimens at the Mayo Clinic and Campbell found the frequency of pulmonary stenosis in 1 130 cases of congenital heart disease to be 10 per cent or 113 cases Abrahams and Wood found 71 cases of pulmonary stenosis in 689 cases of congenital heart disease an incidence of 11 6 per cent

However the association of pulmonary stenosis with intact ventricular septum but with interatrial communication is less common Among the 24 cases of Wood mentioned above there were atrial septal defects in 5 an incidence of 2 5 per cent Campbell noted that of his 113 cases with pulmonary stenosis 41 were cyanotic that is 6 per cent of the total series Of Abrahams and Wood s[1] 71 cases of pulmonary stenosis there were atrial septal defects in 15 including 8 cases in which there were reversed interatrial shunts

Following Fallot s[4] description of 7 cases of pulmonary stenosis with intact ventricular septum and interatrial communication this lesion has been known as the trilogy of Fallot

The age to which patients with the trilogy of Fallot may survive has been mentione

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in several surveys. In 1949 Selzer and associates[7] reviewed the reports of 29 autopsied cases of the trilogy and found the average age of the patients to be 20 years. Soulié and associates[18] quote Tinnit who in 1950 found 11 cases in which death occurred between 20 and 30 years, 3 between 30 and 40 years, and 5 between 50 and 60 years. They also quote Cuvot who in 1945 recorded 7 cases in which death occurred between 20 and 30, 1 between 30 and 40, and 3 between 50 and 60 years. They themselves in their series found 10 cases in which death occurred between 20 and 30 years, 5 between 30 and 40 years, and 1 in which death occurred at 44 years.

A number of individual reports of longevity with this disorder are on record. White and associates reported the case of one of the oldest patients, a man who died at the age of 75 years. Gerier and associates reported the case of a man who died at 53 years. Vogelpoel and associates included in their series 2 cases of patients who lived to be 42 and 49 years. The cyanosed patients living to the age of 44 and 42 years reported by Lorner Soler and associates and Gadboys and associates, respectively, had pulmonary stenosis with closed ventricular septum. Swan and associates[12] included in their series of 22 patients a man who lived to the age of 50 years.

Long-term survival in cases of trilogy of Fallot would not be unexpected when the pulmonary stenosis was slight to moderate, but the following report of a patient surviving to the age of 71 years is of interest because of the high degree of stenosis.

Case report

The patient, a woman, was first admitted to hospital at the age of 68 years. In childhood she had been breathless with effort and susceptible to respiratory infections but she was not then cyanosed. She had not been greatly handicapped by dyspnea and had worked as a dress[maker], domestic servant, and a machinist. She married when she was 25 years old and became pregnant three times, miscarrying twice, and finally being delivered of a full-term infant. When she was 31 years old she underwent an operation for correction of retroversion of the uterus. This procedure was complicated by an episode of congestion of the lung. At about middle age she developed increasingly severe attacks of bronchitis and her effort tolerance progressively declined. Cyanosis was first noted at this time. In her later years cyanosis deepened and her range of activity became progressively more limited. At the time of admission to hospital she had been [bed]ridden for some years.

When examined she was not dyspnoeic at rest. There was marked cyanosis but no clubbing. The pulse was irregular and the blood pressure was 200/100 mm. Hg. The jugular venous pulse showed prominent waves. The venous pressure was not elevated nor was the liver enlarged. There was slight ankle and sacral edema. The lung bases were clear. The apex beat was in the fifth left intercostal space in the anterior axillary line. There was a long systolic murmur of moderate intensity, widely conducted and best heard at the pulmonary area. The second sound was single and faint.

The hemoglobin was 16.9 Gm. per 100 ml. The erythrocyte count was 6,200,000 per cu. mm. The sedimentation rate was 2 mm. in 1 hour. The electrocardiogram (Fig. 1) showed the pattern of incomplete right bundle branch block and atrial flutter with some degree of right ventricular hypertrophy. The chest roentgenogram revealed slight cardiac enlargement with a cardiothoracic index of 61 per cent.

During the first 4 weeks of her admission the edema disappeared, the cyanosis lessened. She became ambulant again and was discharged.

Nine months later she was again admitted in mild congestive failure with the same symptoms, [and] with signs of a recovering hemiparesis involving her left leg. During this admission the arterial oxygen saturation was 84 per cent at rest. With digitalis and diuretics the signs of failure resolved and she was again discharged.

Over the next 3 years her course was one of progressively deepening cyanosis and decreasing activity, with one mild episode of congestive failure. When she was admitted for the last time, at the age of 71 years, her electrocardiogram showed atrial flutter with an irregular ventricular response. Radiologically the heart size had increased and the pulmonary artery had become more prominent. She died some days later during the last days.

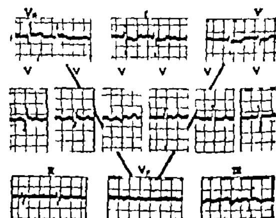


Fig. 1. Electrocardiogram of patient with the trilogy of Fallot showing atrial flutter with irregular ventricular response, moderate right ventricular hypertrophy, and incomplete right bundle branch block pattern.



Fig 2 Heart of patient with the trilogy of Fallot showing the right ventricular hypertrophy

he remained extremely cyanosed and in moderately severe congestive failure

At postmortem examination the heart weighed 590 grams (Fig 2) Both ventricles were markedly hypertrophied the right ventricular wall was 11 mm thick and the left ventricular wall was 16 mm The pulmonary valve showed dome-shaped fusion of the cusps which reduced the central lumen to a diameter of 5 mm (Fig 3) This lumen was further narrowed by firmly attached vegetations making the effective outflow tract 3 mm in diameter The pulmonary artery was dilated beyond the stenosis There was a small atrial septal defect 3 mm in diameter and the foramen ovale was patent The heart was otherwise normal the ductus arteriosus was obliterated On histologic examination the vegetations on the pulmonary valve were found to be consistent with an old healed bacterial endocarditis

Discussion

The most important factor governing longevity in patients with trilogy of Fallot would appear to be the severity of the pulmonary stenosis In our patient there was necropsy evidence of at least moderate constriction of the pulmonary valve the diameter initially was probably 5 mm and this was subsequently constricted to 3 mm by fibrotic vegetations This aperture may be compared with the 3 mm opening in White s[3] patient who was 75 years old and the 8 mm opening in Gerici s[2] patient who was 53 years old The patients whose cases were quoted by Vogelpoel by Torner Soler and by Gadboys[11] were alive at the time of reporting The size of the lumen of the valve was not stated in Swan s case

In our patient cyanosis did not appear until middle life but had been present for many years before death It is possible that it followed the encroachment of vegetations on the lumen of the valve Although Campbell commented that cyanosis tended to be later in appearance in the older patients other reports would suggest that the age of onset of cyanosis does not closely relate to the prognosis in Campbell s older cyanosed patients (20 to 33 years) the usual time of onset was between 12 and 16 years Swan and associates in their series of 22 patients with the trilogy found that 18 were cyanosed before 12 years and 4 became cyanosed after 10 years of age The 44 year old living patient of Torner Soler[1] became cyanosed at 38 years of age and the 42 year old patient of Vogelpoel be



Fig 3 The pulmonary valve of patient with the trilogy of Fallot seen from above

c tme cy inosed it 40 years On the other hand White s 75 year old man w is blue from the time of his early youth Calboy s[1] 42 year old living patient w s termed a blue baby at birth and Vogelpoel s[4] 49 year old patient w is cyanosed at 10 years of age Cericr s[2] 53 year old patient w is never cyanosed

The interatrial communication in our patient consisted of a septal defect as well as a patent foramen ovale Selzer and Carnes[18] in 1953 reviewing cases of pulmonary stenosis concluded that when an interatrial communication is present it is almost always a patent foramen ovale Campbell thought that quite frequently the defect was not a foramen ovale and certainly the presence of both in our case would support him

Tetralogy of Fallot

The tetralogy of Fallot presents a wide spectrum of clinical pictures ranging from the deeply cyanosed severely limited patient to the patient with the so called acyanotic form of this defect Because of this diversity of presentation series of unselected cases may not be representative of all variants of this condition and the figures quoted for average survival may have little significance in the assessment of prognosis in the given individual Maud Abbott[1] estimated the average length of life to be 6 years if the pulmonary artery showed atresia and 12 years if it was stenosed Donzelot and associates[23] in 1949 reporting cases in 200 living patients found that 13 patients were between the ages of 21 and 30 years and that 1 patient was 45 years old Guyot[19] in 1945 reviewing 81 cases found that 16 patients died between the ages of 20 and 30 years 2 died between 30 and 40 years and 1 was alive over 40 years Soulie and associates[20] in 1956 studied 144 patients with this defect all alive except 4 and found 8 between 20 and 30 years of age 2 between 30 and 40 years and 2 over 40 years

A number of reports of individual cases in which survival was prolonged into adult life are in the literature In 1871 Bock reported the case of a patient who died at 40 years of age the oldest patient in the series which Fallot reported in 1888[4] died at 36 years of age and until White and Sprague[24] in 1921 described their famous musician who lived to the age of 59 years no survivor to an older age had been found Since then 21 other patients surviving over the age of 40 have been reported

Case report

A 68 y ar old woman w dmitted t hospital be au of gradually incre ng confusion fainting and hest p She had been told in childhood th t he had hole i her heart and long she ould remember he had been cy nosed I dyspnea on xertion A a chil I he could w lk slowly without discomfort but dyspnea followed en light effort I w best relieved by squatting I pisodes of ncon ciousness sometime accompa ied exertion n hot w ather but these became less frequent in dult l f Between the ges of 17 and 21 y she w ld t h r mproved She was employed t che from the ge of 19 y rs When he w 35 y rs 11 she emigrated from Engl nd t N w Z aland and continued te ching until her retirement n her l t fift During her l ter l f effort ed irregul r palpit t on and the oc urrence of sharp tt ck of retrosternal p in tw or three times d ily

O adm ion t hospit l she moderat ly d spneic t rest nd was severely cy n ed There w ly slight clubbing of the fingers She h d a marked thoracic k phc oliosis and a prominent pr cordium The pul e w s irregul r w th multiple t systoles The blood pres ure s 140/90 mm Hg The jugular enous pre re w elev t d 5 cm bov the stern l gle nd the h er w s palpable tw fingerbre dth below the cost l margin She had moderat kle nd cr l edema and bilateral crepitation t he lung b se The pe be t s in the ighth left int rcost l sp to the posterior llary line A ry loud s tol murmur om panied by thrill w udible dow the left sternal dge nd w he rd well also t the pe The second

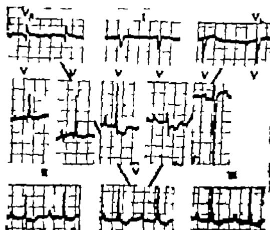


Fig. 4. Ele trocardiogram of patient with tet alogy of F llot showing P pulmonale and right entricular dominance



Fig. View into the right ventricle of heart with the tetralogy of Fallot showing the right ventricular hypertrophy, the ventricular septal defect (*lower arrow*) and the right ventricular outflow tract (*upper arrow*) with the cone-shaped pulmonary valve above.

sound was faint and single. No abnormality was found in the other systems.

Laboratory findings included a hemoglobin of 18 Gm. per 100 ml., hematocrit of 56 per cent, and sedimentation rate of 1 mm. in 1 hour. The electrocardiogram (Fig. 4) showed at least moderate right ventricular dominance, prolongation of the P-R interval, and P pulmonale. The chest roentgenogram confirmed the presence of gross cardiac enlargement and displayed a right-sided aortic arch.

Mental confusion and apathy were the outstanding features of her condition. Although the signs of congestive failure largely cleared with digitalis and diuretics, her condition gradually deteriorated. During the 6 weeks of her stay in hospital she experienced a series of collapses in which she became gray in color, her blood pressure fell, and she remained comatose for as much as 2 days. On two occasions these attacks were precipitated by being sat up out of bed. She died in coma 6 hours after the onset of one of these attacks.

At postmortem examination the heart weighed 312 grams. Both ventricles were hypertrophied; the average thicknesses of the right and left ventricular walls were 14 and 18 mm., respectively (Fig. 5). The aorta overrode a high interventricular septal defect 14 mm. in diameter so that two thirds of the aortic opening faced the right ventricle. The pulmonary valve (Fig. 6) showed fusion of the thickened cusps to form a dome-shaped diaphragm with a central opening which measured 10 by 8 mm. There was no infundibular stenosis. The main pulmonary arterial trunk and both branches were dilated; the walls of the vessels were of normal thickness. The ductus arteriosus and the foramen ovale were both closed. The aortic and mitral valves were normal. The coronary arteries were patent and in the normal anatomic situation. The pulmonary veins and venae cavae were normal.

Discussion

Twenty of the reported cases of Fallot's tetralogy with survival of the patients to over the age of 40 years have been studied.

Of the patients whose ages were stated, 3 were over 60 years, 10 were between 50 and 60 years, and 9 were over 40 years. The oldest was a 69-year-old man and the oldest woman whose case was previously reported was 64 years of age. Only 4 patients, aged 56, 53, 52, and 45, were alive when their cases were reported.

Ten patients were males, 7 were females, and in three reports the sex was not stated.

Six patients were cyanosed at birth and 4 had been blue as long as they could remember. One patient was known to be cyanosed at 32 years of age and was moderately cyanosed when he was reported alive at 56 years. Three patients did not develop cyanosis until middle life: in one, cyanosis appeared after pulmonary tuberculosis; another became cyanosed at the onset of congestive failure 3 years before his death, and the third developed cyanosis intermittently in middle age and was only slightly cyanosed at the



Fig. 6. The pulmonary valve of heart with the tetralogy of Fallot seen from above. The forceps are behind the valve leaflet.

time of his death In 2 other cases[19,1?] the age of onset of cyanosis is not given both patients were cyanosed at the time of death One patient[29] was never cyanosed even at the time of death It was not possible to find a relationship between the severity or age of onset of cyanosis and the length of survival Certainly the patient[6] who survived the longest was a man (aged 69) who became cyanosed only intermittently after middle age On the other hand one patient[21] who had marked cyanosis and clubbing died at the age of 64 years and our patient who had been cyanosed as long as she could remember lived to 68 years

Clubbing was present in 15 patients and where graded was marked in 5 moderate in 2 and slight in 1 There was no clubbing in 2 patients and the presence or absence of clubbing was not mentioned in the other reports The degree of clubbing was closely paralleled by the intensity of cyanosis and by the height of the red blood cell count All 5 patients with marked clubbing were cyanosed from their early youth

Most patients were very much limited by shortness of breath but nevertheless were capable of a wide range of activity Two[17] were always dyspneic at rest Two[1] were dyspneic with slight exertion one of these was a musician who had also worked as a painter and a clerk and who undertook a trip from America to Europe Five were dyspneic only with greater exertion 2 of these worked as laborers one also as a coal miner and building superintendent One was a manageress of a restaurant and one was an accountant Eight patients whose effort tolerance was not defined followed various occupations including those of an electrical engineer a seamstress a journalist a racing driver and a night watchman whose duties involved climbing seven flights of stairs nightly One of these had played football as a boy another[6] described himself as quite a runner in his day One patient[7b] when first reported upon at the age of 26 years was always short of breath but when described again at 52 years was not unduly dyspneic A number of patients had successfully undergone operations including tonsillectomy cholecystectomy tooth extraction sterilization and orthopedic operations One[21] underwent electroconvulsive therapy and one woman had had two normal confinements at 32 and 35 years of age

The presence of cyanosis and the degree of dyspnea were not necessarily related For example 2 patients who showed no clubbing or polycythemia and who developed cyanosis either late or not at all had both been dyspneic as long as they could remember and had become very dyspneic with effort On the other hand 2 patients[11] who were capable of heavy work and who had been laborers were both cyanosed and had clubbing of the fingers Donzelot[1] also after studying 200 cases of the tetralogy of Fallot commented that no close parallel between the degree of cyanosis and dyspnea could be found

Fan and Fleury[2] remarked that their patient had noticed improvement in her effort tolerance with the onset of puberty and that her condition had gradually deteriorated after the age of 40 One of Soulié's patients[26] became less cyanosed at about 15 years of age Bedford[7b] describes a patient who was less dyspneic at 52 years of age than she had been at 26 and the patient here reported said that she became less dyspneic after the age of 17 at which time she learned to ride a bicycle On the other hand Donzelot[11] found that puberty was a critical time for these patients and sometimes heralded deterioration and death

Although 4 patients had no complaints other than shortness of breath on effort and cyanosis cerebral complications and congestive episodes were common Nine patients suffered congestive cardiac failure which varied in severity from ankle edema to gross congestion In one patient recurrent attacks of congestive failure were associated with episodes of coma and transient neurological abnormalities Hemiplegia developed in 4 patients and 5 patients had symptoms of episodic cerebral ischemia which produced transient paresthesia and weakness of the limbs It seems likely that these attacks were embolic or thrombotic in origin and this tendency was demonstrated in 2 other patients one of whom[4b] developed a popliteal embolus and a pulmonary infarct and the other[27] a femoral vein thrombosis

The most common mode of death was coma In 5 patients this was associated with congestive failure and 2 died after strokes One patient went into anoxic coma without congestive cardiac failure after a respiratory infection One de veloped a right hemiplegia and congestive failure 4 days after operation for relief of a gall stone ileus One[18] died at the age of 41 years of chronic glomerulonephritis one[27] at 53 years of chronic pyelonephritis secondary to a carcinoma of the uterine cervix and one at 47 years from carcinomatosis originating in the bladder One had a pulmonary infarct at 47 years of age after a leg was amputated for a popliteal embolus One patient died suddenly an unexplained death Two deaths were not detailed and 4 patients were still alive when their cases were reported

In only 10 cases were the radiologic appearances described In 8 cases cardiac enlargement was demonstrated and one heart[11] was not radiologically enlarged

At postmortem examination the hearts were all enlarged the weights ranged from 370 to 970 grams the former figure being in a woman The average weight was 606 grams The maximum thickness of the free right ventricular wall ranged from 10 to 20 mm (average of 10 = 15 7 mm) and that of the left ventricular wall also ranged from 10 to 20 mm (average of 9 = 15 8 mm)

The pulmonary stenosis was valvular in 5 hearts infundibular in 3 and a combination of the two in 5 One pulmonary artery ended blindly 1 cm from the pulmonary valve the pulmonary blood supply was through a patent ductus arteriosus The lumen of the outflow tract ranged from 12 to 240 sq mm in 6 valves and from 30 to 390 sq mm in 6 infundibula A striking feature was the frequency of bicuspid pulmonary valves 10 hearts showed this variation

The area of the ventricular septal defects ranged from 78 to 1 500 sq mm in 11 cases one other admitted a thumb 2 admitted two fingers and 2 were described as large

The degree of overriding of the aorta was estimated in various ways in 3 hearts there was one third overriding in one the aorta overrode the left ventricle more than the right in one the aorta arose from the right more than from the left in 2 there was two thirds overriding and in one[1] the aorta arose entirely from the right ventricle

A number of associated cardiac malformations were noted in the case[13] in which the pulmonary artery terminated in a blind end above the valve the ductus arteriosus carried blood to the lungs In no other case was the ductus patent The foramen ovale was present in 4 hearts it was described as slit like in 1 and in the other 3 was accompanied by a valve which was apparently capable of anatomic closure In one heart the aortic valve had four cusps and in another it was bicuspid Calcific aortic stenosis was present in one case accompanied by tricuspid calcification and atheroma of the aorta A right sided aortic arch was seen in 2 patients

There was a wide range of severity of heart deformity in these patients with Fallot s tetralogy but no constant relationship could be found between the degree of deformity and longevity of the patient The severity of symptoms during life could not be correlated with the anatomic findings nor did the degree of right ventricular hypertrophy relate to the size of the septal defect or to the lumen of the pulmonary valve For example of 2 hearts of similar weight and with a septal defect of the same size that which had the largest pulmonary passage and the least aortic overriding had the greatest degree of right ventricular hypertrophy The anatomic findings could not be correlated with the severity of clubbing or polycythemia

Summary

With the development of surgical techniques which allow correction of most congenital heart defects the opportunity to study the natural history of these lesions is being lost Geriatric units are possible sources of instances of long term survivals Two cases of cyanotic congenital cardiac disease are reported from a geriatric unit One patient with the tetralogy of Fallot who survived to the age of 68 years is believed to be the oldest woman whose case has been reported The other patient who

survived to 71 years had the trilogy of Fallot. A review is made of previous reports of survival beyond the age of 40 years of patients with these conditions.

I would like to thank Dr. J. L. Newman for permission to report these cases and Dr. J. C. I. Williams for assistance with presentation.

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*References 14-31 cover the reported cases of tetralogy of Fallot with survival over 40 years of age, with sex and age of the patient given.

Clinical pathologic conference

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Clinical abstract

History An 11 year-old boy was first admitted to Cleveland Clinic Hospital on Dec 1 1955 because of dyspnea He had been in apparent good health until 1 year before admission when he had acute illness characterized by fever headache and aching in both thighs These symptoms persisted for 1 month before he was hospitalized in another institution

On admission there his temperature was 103 6 F and his pulse rate was 120 The heart was enlarged and loud systolic apical murmur was noted A questionable diastolic murmur was recorded The urine was normal the erythrocyte count was 3 350 000 per mm the hemoglobin 10 5 Gm per 100 ml and the leukocyte count was 15 50 per c.mm with differential count of 71 per cent polymorphonuclear leukocytes 1 per cent band cell 26 per cent lymphocytes 1 per cent monocytes and 1 per cent eosinophil The results of spinal fluid studies and blood cultures were normal An electrocardiogram showed P R interval of 0 19 to 0 20 second and tendency toward right axis deviation A roentgenogram of the chest revealed evidence of grossly enlarged heart Treatment with penicillin cortisone and aspirin was instituted and within 4 days his temperature was normal Penicillin therapy was continued for 13 days Six days after discontinuance of penicillin his temperature had risen to 104 6 F and the use of the drug was resumed Within 18 hours his temperature was normal Penicillin was given daily for 4 days and twice weekly thereafter Cortisone was continued until March 9 195 and he was discharged from the hospital on March 21 with instructions to rest at home prophylactic penicillin was to be continued

He was admitted to the hospital because of a cough in June 1955 and again on July 5 1955 Radiographic examination revealed enlargement of the heart and the shape thought to be suggestive of pericardial effusion The cough cleared rapidly with the use of low salt diet digitalization and the administration of mercurial diuretics Penicillin was administered during and after hospitalization and digitalization was maintained Subsequently he was reported to have had occasional pulmonary edema that responded well to the use of mercaptomerin sodium and acetazolamide On Nov 29 1955 he was lethargic and his face was edematous although there was no edema elsewhere Tests showed hyaline casts in the urine hemoglobin 8 5 Gm per 100 ml and leukocyte count of 12 900 per mm The electrolytes were normal but the nonprotein nitrogen was 67 mg per 100 ml He improved slowly with diuretic therapy and was transferred to Cleveland Clinic Hospital on Dec 17 1955

Physical findings On admission his temperature was 99 4°F the pulse rate was 116 and the blood pressure was 118/78 mm Hg He was well developed but thin There was prominent precordial bulge The heart appeared to be considerably enlarged A striking apical systolic thrill was palpable The pulmonic second sound was accentuated There was Grade 5 apical systolic murmur this murmur was transmitted to the back the forearms and even to the patellae A Grade 1 or Grade 2 early blowing diastolic murmur was heard along the left border of the sternum The spleen was palpable but the liver was not palpably enlarged

Laboratory findings The results of tests were normal urine hemoglobin 12 3 Gm per 100 ml the hematocrit reading 42 ml and leukocyte count 5 300 per mm The serum electrolytes were normal and the blood urea was 27 mg per 100 ml A corrected erythrocyte sedimentation rate was normal tests were negative for C reactive protein and for lupus erythematosus The electrocardiogram is shown in Fig 1 1 Roentgenograms (Figs 2A C) of the chest showed evidence of enlargement of all chambers of the heart and on fluoroscopic examination there was intrinsic pulsation in the hilar areas

Course The patient was discharged on the fifth hospital day and was readmitted on J 2 1956 for cardiac catheterization and angiocardiography The right ventricular pressure was 72/2 and the pulmonary arterial pressure 75/46 mm Hg

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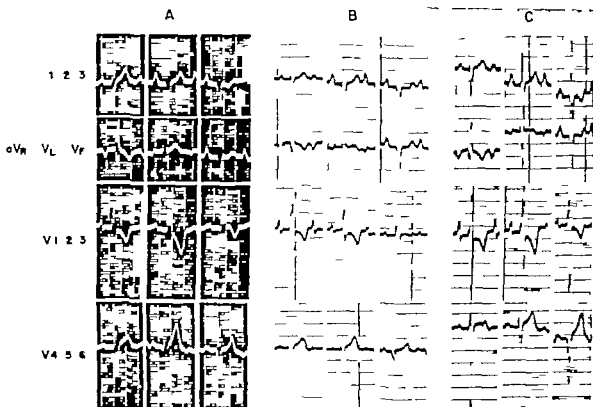


Fig 1 Electrocardiogram *A* December 1955 *B* Aug 1 1957 *C* May 20 1958

The wedge pressure w 2 mm Hg N evidence of sh t could be demonstrated by oxygen satura tions or cineangiocardiograph H was discharged t return to schedul of bed and chair rest t home *H was gi en 1 w salt diet digitalis nd Gantrisi* daily One ear later he was re-examined nd seemed to be much improved he had no complaints Exam ination sh wed no significant changes from the pre ious findings except that the pleen was not palpable A roentgenogram of the chest showed that the transverse diameter of the heart had increased 2 5 *cm in the 13 months ince the time of his previous* tudies He wa examined again on Aug 1 1957 because of dy pnea during rapid walking and few attacks of paroxysmal nocturnal dy pnea Exam ination showed no ignificant changes from the previous findings except that there were few rales present at the base of the right lung An electrocardiogram is how Fig 1 B

On May 20 19 8 he as examined because of mild dyspnea nd history of ha ing had epi sode of severe dy pnea bdominal pain nd h er swelling Râles and rhonchi were heard i both l ng fields but there were no other ignificant devia tions from the previous phy ical findings An elec trocardiogram how Fig 1 C It w decided to recheck cardiac catheterization nd cineangiocardiography in order to determine the presence or absence of a shunt He readm tted to the hospital July 6 1958 He was dy pneic and edema tous on adm sion nd cardia catheterization was deferred because of the presence of congestiv heart failure An electrocardiogram was similar to that of May 20 1958 except that trial fibrillation had de eloped Roentgenograms of the chest (Figs 3 1 C) howed evidence that the heart had *ncreased in size the tra erse diameter being* 18 2 cm During the following night when he rose from bed to use a urinal he fell nd died imme diately

Discussion

DR PROUDFIT Mitral insufficiency appears to be the predominant le ion in this case The physical findings are consistent with that diagnosis Mitral insufficiency of marked degree may be manifest by a loud systolic murmur that is widely dis tributed There was radiologic evidence of left atrial and left ventricular enlargement No mention was made of systolic expansile pulsation of the left atrium The pulsation of the hilar vessels is peculiar and may represent pulsation in the pulmonary veins *especially in view of the fact that no* cause for high pulmonary blood flow was demon strated The catheterization findings are *suggestive of mitral insufficiency* Finally atrial fibrillation developed late in the course of the disease

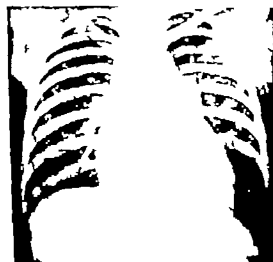


Fig 2A Posteroanterior chest film taken on J 4 1956



Fig 2B Right anterior oblique chest film taken on Jan 4 1956

The electrocardiograms in this case are interesting The reported tendency toward right axis deviation in the electrocardiogram taken 1 month after onset of his acute illness suggests the presence of long standing disease Our original record (Fig 1 A) shows notched high voltage P waves a P R interval of 0 2 second right axis deviation and large R waves with delayed intrinsicoid deflections in Leads V and V These findings are indicative of enlargement of both atria and right ventricular hypertrophy Leads V and V_6 show interesting changes There is a Q wave before a small R wave in Lead V_5 and a slurred Q wave before a small R wave in Lead V The intrinsicoid deflection is delayed in Lead V There were inverted U waves in Leads V V_5 and V these may be seen in left ventricular hypertrophy The inverted U waves persist in subsequent records An electrocardiogram of Aug 1 1957 (Fig 1 B) shows a decreasing voltage of the R waves in Leads V and V and a delayed intrinsicoid deflection in Lead V In the record of May 20 1958 the R wave is absent in Lead V—a finding seen occasionally in severe right ventricular hypertrophy

The cause of the mitral insufficiency is the real diagnostic problem In the differential diagnosis rheumatic valvulitis perforation of a leaflet or rupture of a chorda tendinea as a result of bacterial endocarditis and congenital deformity involving the mitral valve must be considered The history of the acute illness is not typical of rheumatic fever There was a systolic murmur present at the time of the patient s first medical examination Unfortunately it was not noted whether a precordial bulge was present then although it was stated to



Fig 2C Left anterior oblique chest film taken on J 4 1956



Fig. 3A. Posteroanterior chest film taken May 21, 1958.



Fig. 3B. Right anterior oblique chest film taken May 21, 1958.

be present subsequently on admission to Cleveland Clinic Hospital. A precordial bulge would have indicated long-standing cardiac disease and would have been consistent with congenital heart disease or rheumatic heart disease acquired earlier in life. The evidence of a greatly enlarged heart on radiographic examination at the time of the original study must indicate long-standing disease, severe myocarditis, or pericardial effusion. There is nothing to suggest strongly the latter possibility. The absence of notation of the usual criteria for diagnosis of active rheumatic fever is disturbing. It seems likely that if he had had acute rheumatic myocarditis he must have had pre-existing rheumatic heart disease in view of the fact that he had marked cardiac enlargement and right axis deviation in the electrocardiogram at the time of his original examination, even though his illness had been of short duration. Congestive failure was an early and rather persistent manifestation until death. It would seem to be necessary to assume that this boy had previous rheumatic heart disease if the illness was of rheumatic origin and that the terminal illness was due to recurrent disease with active myocarditis. It is difficult to be sure that myocarditis was present, however. A firm support for the diagnosis of rheumatic heart disease cannot be established.

It is possible that this patient had acute bacterial endocarditis to account for his original illness, although later blood cultures were negative. Acute endocarditis can cause perforation of the mitral valve



Fig. 3C. Left anterior oblique chest film taken May 21, 1958.



Fig. 4. Photograph of gross left atrial and ventricular chambers showing the large fenestration in the anterior leaflet of the mitral valve.

or rupture of a chorda tendinea resulting in mitral insufficiency. This could account for the development of congestive heart failure which was a subsequent problem. It is possible that he had a penicillin-sensitive organism and that he received sufficient treatment to arrest the infection even though treatment was not intensive. The presence of severe cardiac enlargement and the electrocardiographic changes early in his illness are important evidence against this diagnosis.

Congenital mitral insufficiency as an isolated lesion is rare. It seems likely that this boy did not have any atrial septal defect or valvular lesion of congenital origin. Most commonly, mitral insufficiency is associated with septum primum defects. Certainly, the possibility of congenital mitral insufficiency cannot be excluded. It would be difficult to explain on the basis of congenital disease the acute illness that heralded his disease clinically. On the other hand, the extreme cardiac enlargement and electrocardiographic changes present early in the illness, the precordial bulge noted later, and the relentless course of his disease would be consistent with congenital heart disease.

In conclusion, mitral insufficiency is the structural lesion of the heart. The valvular defect may have been of rheumatic or of congenital origin. Although there was no certain evidence of rheumatic myocarditis, I think that the insufficiency is more likely to have had a rheumatic than a congenital basis.

DR. MCCORMACK. Many of you will remember that some months ago we presented an unusual cause of aortic insufficiency resulting from rupture of a semilunar valve. I could not resist presenting another unusual case of valvular insufficiency involving in this instance the mitral valve.

The heart was globular and much enlarged; it weighed 640 grams. The epicardium was everywhere glistening and transparent. The globular shape was in part due to an enlarged right ventricle. When the heart was opened, the right ventricle and both atria were markedly dilated. The myocardium was reddish brown and firm. The right ventricle varied from 0.1 to 0.3 cm. in thickness and the left ventricle at its maximum measured 1.3 cm. in thickness. The aortic, tricuspid, and pulmonary valves were normally formed, thin, and without distortion. The anterior leaflet of the mitral valve was remarkable (Fig. 4). Near its base was a round fenestration which measured 1.5 cm. in diameter. The edge of this fenestration was slightly thickened, but there was no evidence of any attachments to it. The remainder of the mitral valve was normal anatomically with delicate pliable margins and thin, discrete chordae tendineae. Scattered over the walls of the left atrium, both in the region of the valve and on the posterior surface, were numerous endocardial thickenings representing multiple so-called jet lesions. Some of these were scimitar-shaped, but others represented mainly endocardial thickening. Microscopically, there was no evidence of any pre-existing rheumatic heart disease in so far as changes in the atrioventricular angle, vascularity of valves, or myocardial scarring were concerned. The cardiac fibers were slightly enlarged and possessed large angular nuclei.

The lungs weighed 1,000 grams and were firm and slightly brown. Microscopically, they showed all the features of chronic passive congestion; the pulmonary vasculature was only slightly increased in prominence. The liver also showed the features of chronic passive congestion.

I should then at least attempt to explain the presence of the perforation within the anterior leaflet of the mitral valve. There

are three possibilities for this occurrence The one that I slightly favor is that it represents a congenital failure of formation of the valvular leaflet The lesions that most resemble this physiologically and possibly anatomically are those that occur in association with a persistent ostium primum defect The changes in the mitral valve in those instances however usually are manifested as clefts in the valve with free margins that may or may not be bound to the ventricular wall by shortened chordae It is a lack of recognition of these clefts that may be responsible for mitral insufficiency after complete repair of the septal defects present The second possibility also congenital is a variation of the anomaly double orifice of the mitral valve However no signs of leaflets or accessory chordae tendineae were found A third possibility would be that of a most unusual form of healed bacterial endocarditis with the point of bacterial lodgment being high on the valve rather than along the valve margins as usually seen However nothing in the clinical history prepares us for this eventuality and if such is the case it is a most fortuitous set of circumstances A lack of vascularity and other signs of previous inflammation also lessens the possibility of such an origin In any event there were no stigmata of previous rheumatic heart disease that we could demonstrate

To summarize then the anatomic findings in this case are idiopathic fenestration of the mitral valve with associated jet lesions and marked cardiomegaly resulting in severe mitral insufficiency Evidences of cardiac failure were found in the lungs and liver in the form of chronic passive congestion

Diagnosis Valvular insufficiency due to idiopathic fenestration of the mitral valve

Annotations

Patent ductus in infancy

Many children present with symptoms of cardiac failure in the first year of life and a proportion of these will be found to be suffering from patent ductus arteriosus. It is important to distinguish this group since prompt operation can be both lifesaving and curative. These children frequently present with feeding difficulties, failure to thrive, or as breathless babies, and it is not until a careful examination of the chest is undertaken that the presence of a cardiac murmur focuses attention on the heart as a possible cause of the symptoms.

Evidence of some degree of congestive failure such as increase in venous pressure, hepatomegaly, or obvious dyspnea at rest is very frequently present. When such signs are found intensive medical therapy should be initiated without delay, and operation should be deferred until the cardiac failure has been adequately controlled with appropriate medical therapy. Not infrequently an infection of the respiratory tract initiates cardiac decompensation, and when there is any suggestion that this is so appropriate antibiotic therapy should be commenced without delay. In general these children show a prompt and gratifying response to treatment, and one can then proceed to operate, but *it is most unwise to undertake operation* in these cases before controlling any degree of cardiac failure which may be present.

In this age group the auscultatory findings are rarely typical and the presence of a fully developed continuous murmur is unusual. Reliance must be placed on the peripheral signs. The presence of palmar pulsation and of a wide amplitude peripheral pulse is always very suggestive of the presence of patent ductus arteriosus. The electrocardiogram will usually show evidence of left ventricular strain unless pulmonary hypertension or some other complication is also present, and radiography will demonstrate marked cardiomegaly with obvious evidence of a substantial left-to-right shunt. In general no additional investigations should be carried out in these cases since the children are usually seriously ill and to undertake such procedures as angiocardiography or cardiac catheterization may well militate against survival.

We have always adopted the attitude that if patent ductus cannot be reasonably excluded on clinical examination these children should be submitted to exploratory thoracotomy. In practice reliance on the peripheral signs and careful appraisal of the clinical signs that are present will usually result in a correct diagnosis by an experienced cardiologist.

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Erythrocytosis and ischemic myocardial disease

It is generally recognized that both venous and arterial occlusions occur frequently in polycythemia vera. Coronary artery thrombosis has been reported in from 6 to 25 per cent[4] of patients with this disease and treatment with radioactive phosphorus is said to decrease the incidence of coronary thrombosis. This would suggest that the association of coronary thrombosis and polycythemia is not mere coincidence. The patients reported in the literature usually have well-established erythremia. Yet there are patients in whom moderate erythrocytosis exists in association with coronary artery disease and in whom the erythrocytosis is usually ignored.

In this group of patients it is difficult to know what influence the erythrocytosis has on the production or the course of myocardial ischemia. The increased viscosity of the blood would be expected to place a stress on the heart and result in some impairment to coronary flow. Possibly in part because of the increased viscosity of the blood many of these patients have mild arterial hypertension.

Examination of the clinical records of such individuals suggests that the erythrocytosis has an adverse effect on coronary blood flow. We have recently evaluated 12 patients with coronary artery disease and packed red cell volumes ranging between

50 and 54 per cent (mean 51 per cent). The patients ranged in age from 39 to 66 years (mean 47 years); 5 were less than 45 years. All had angina and 3 had clinical and electrocardiographic evidence of myocardial infarction. *The hematocrit was lowered to within normal levels by* venesection in 3 of the 12 patients, and there was definite clinical improvement in each patient in that the frequency of the anginal attacks decreased. In one of the 3 patients with *arterial hypertension in addition to erythrocytosis* the blood pressure fell to normal after venesection.

Although all of the patients were in the arteriosclerotic age group, the fact that half of them were less than 45 years of age may be of significance. The etiology of the erythrocytosis was not always evident. The other formed elements of the blood were not increased, although minimal splenomegaly was present in 3 patients. In one of the 12 patients the polycythemia was probably secondary to pulmonary disease. The bone marrow was studied in 2 patients and was found to suggest early polycythemia vera. No definite etiology for the erythrocytosis was apparent in the other patients. Whether or not they represent instances of early or mild polycythemia vera or merely normal variation in erythrocyte values is not known. Whatever the etiology, it appears that even moderate erythrocytosis exerts a deleterious effect on the cardiovascular system of some individuals. Thus, in the cardiac patient it is probably wise to consider the erythrocyte concentration and to reduce even moderately elevated hematocrit to mean normal levels, that is, to about 45 per cent. Detailed clinical studies of such patients are needed in order to determine the extent to which moderate erythrocytosis may produce myocardial ischemia.

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Reliability of the indicator dilution technique

Though an isolated measurement of cardiac output has little specific diagnostic value, it is an important physiologic variable, the use of which permits the calculation of such parameters as stroke work, stroke volume, stenotic valve areas, and total peripheral resistance. When the dye-dilution method is employed to measure flow, additional data may be derived, such as the mean transit time and a number of central blood volumes—depending upon which pair of injection and collection sites is used. The wide popularity of this technique in recent years is related to its convenience, applicability to many types of sick and well patients, and its suitability for use in transient "steady states." Many reports of studies in which the dye curve was utilized are prefaced by justifying statements holding that the cardiac output measured by this method is reproducible, accurate, and that it checks well with those determined by the Fick principle. Although the literature reveals no systematic difference, there is little evidence to support an argument for a high degree of reproducibility, accuracy, or consistent checks against the Fick method.

Two hundred and seventy-eight tabulated pairs of cardiac outputs as measured by the Fick and indicator-dilution techniques of various types both in human beings and dogs have been reviewed from the literature. Analysis of these comparisons reveals that two standard deviations of the differences is ±40 per cent of the mean cardiac output for the group. Similarly, there are 241 graphed but not tabulated pairs, and the scatter of these differences is of the same order of magnitude. The nature of this variability can be found in an analysis of 36 tabulated and 31 graphed indicator dilution studies done in duplicate. This demonstrates that the dye method is reproducible only to ±24 per cent (two standard deviations). A similar error is said to exist for the Fick method. The explanation for the poor reproducibility of the cardiac output by the dye-dilution technique probably resides in both methodological errors and changes in the patient's state between determinations. Unfortunately, there has been little published regarding the magnitude of either of these factors. In their classic combined study in 1948, Hamilton, Cournand, and their respective groups reported variations of weighing and pipetting that could result in 6 per cent error if each were in the same direction. More recently, duplicate cuvette densitometry has been used in man to record 266 paired curves after a single injection of indicator from the same and different arteries. These studies have shown that two standard deviations of variation from the same artery was ±430 c.c. per minute. On the assumption of a mean cardiac output of 6 L. per minute, this variation would be approximately ±8 per cent. The variability of the cardiac outputs calculated from curves recorded at different arteries after a single *injection of indicator* was more than twice this value. These data suggest that errors in instrumentation and variations associated

ith injection collection and incomplete mixing of the indicator can account for more than half f the observed ariation n reproducibility The remainder must be ttributable to lack of steady st te in man and the know changes in cardiac output in anesthetized animals[14] Reduction of the total ariation is difficult and involves the improvement of already advanced technical method Equally difficult is the achievement of greater patient stabil it This latter ma tax the personal skill of the investigator ho to reach this end mu t take the emotional a ell as the radial pulse of his subject

The disturbing coefficients of riation men t oned abov are ell know grudgingly tolerated and not well publicized by orkers in the field pos ibly because there nothing better t the moment to supplant the technique The errors inherent in the dy -dilution method nece sit te that changes in card ac output and all other mathe matically related parameters be large in orde t hav ny significance and m ke these measurements relatively insensitiv t small changes Thus studies in this area may hav t deal with trends rather than p values until something better becomes ailable

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The venous hum

Although mentioned most textbook of cardiology the enous h m perhaps the least studied of card ovascular acoustic phenomena It is important not only because of the high incidence of t oc currence in children (over 50 per cent in some series[1]) but because it ma easil be confused ith murmurs of significant cardiac lesions when the hum in the neck is transmitted downward over the upper chest Under these circumstances unless diagnostic maneu ers designed to obliterate the enous h m are performed diagnosis of paten ductus arteriosus or even aortic insufficiency

be mistakenly entertained I addition the detection of a enous hum may alert the clinician to the possibil ty of anomalous pulmonary enous drainage into the ca al system

Venous hums are best heard over the right supraclavicular area but they can occur over both sides of the neck or solely over the left jugular ein They are loudest in the upright position during in piration nd when the eins are put on the stretch by turning the head to the opposit side The hum disappears w th pressure over the jugular vei or on assumption of the supine position The murmur is continuous and ha a cavernous or roaring quality the pitch of which ma be altered by light pressure w th the stethoscope Inten ity of the murmur increases during dia tole a feature distingui hing the enous hum from the murmur of an arteriovenous aneurysm or a *patent ductus arteriosus* When *enous hums* re transmitted dow ard over the precordium these precordial components can be eliminated by pressure over the right side of the neck and this procedure should be carried out whenever con tinuous murmur is heard over the chest

The exact mechanism whereby the enou hum is produced not completely understood The diminished iscosity of the blood in the case of anemia fa ors t ppearance It frequent occurrence in young children and it accentuation by inspiration or the pright position indicates that factors leading to an increase in the elocity of blood flow in the great eins of the neck are primarily responsible for the hum Other flow murmurs apparently due to increased elocity of blood flow has been demonstrated by intracardiac phonocardiography Placing the neck eins under tension increases the intensity of the hum suggesting that partial enous con triction is contributory mechanism Anatomic dete minants also play an important role in the genes of the enous hum ince the sit of origin of the bru t is t the convergence of several streams of fluid entering the superior ena ca a This may fa or the initiation of periodic wake fluctuations capable of generating sound ibrations well above the threshold of audibility I summary ncreased velocity of blood flow diminished iscosity of the blood partial enous constriction and natomic factors leading to wake fluctu tion are operati singly and in combination in producing the enous hum

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Letters to the Editor

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March 6 1961

To the Editor

There are the impres ions of an American phy si cian on diet coronary theromatosis and related problems in East Africa as gathered on short trip through Africa

During the pa t several years I made thr trips to South nd East Africa as usual I spent some time in siting hospitals clinics prominent intern ists and patholog ts etc w th my special interest being in cardiov scular diseases About two years ago I publi hed de cription of my findings in the *Archives of Internal Medici* (January 1958) A recent nnotation by Dr Whit in this Journal and recent acrimonious controversy between two car diologists in the *Journal of the America Medical Association* has prompted me to rit t you today—all the more so beca my observ tions pertain to slightly different region of Africa ell as to slightly different aspect of the problems

T begin with I found among the natives of South Africa the same rarity of coronary atheroma tosis as others ha found nd de cribed (pecially Bront Stuart G A Elliott etc) However what is frequently overlooked in this connection is that although coronary disease is rare among the Bantu cerebral nd renal well as limb arteriosclerosis is ery common among these people and is quite often fatal Thus unitarian monistic etiological con cept of atheromatosis cannot be defended—unless one accepts the highly ingenios but so far un proved explanation offered by Elliott (in litt) that the heart as an organ which is functioning physically day and day out year in year out has much stronger physical stresses than the other parts of the body mentioned

But perhaps still more interesting is the observa tion that I made in Ethiopia (country which seldom 6 ures in connection with the problems for it is rarely vi ted by our physicians) Ken nd in Uganda ir that even those tribes which are quit carnivorous g the Masai are quit immune to coronary arteriosclerosis Now because of my affec tion for the noblest bra est and (in my opinion) nicest people in Africa the Masai I sited them twice and I could confirm the generally held belief that these epigoni of the really great Africans eat only meat and drink only blood and milk and yet they do not suffer from coronary disease One of Africa greatest internists told me that this is due t the fact that they walk ery much Well Uganda my friend Prof sor Davies certainly one of Africa greatest pathologists was kind enough t how me dozens of hearts (necropsy pecimens) afflicted ith endomyocardial fibrosis (that he so plendidly de cribed) However coronary thrombosis is extremely rare among the natives When seen it occurs in hard orkers Of the only two cases I ha seen one cycled 15 miles day t mar ket his egetabl (in litt)

As the reader ca readily see coronary thrombo is rare mong the Africans both mong the non protein-eating nd among the strictly fat nd meat eating ethnic groups as also among the intermediat groups (Abyssinians) Incidentally in Ethiopi where I ted several places the answer was every where the same the hites ha t the natives do not h t coronary d ease Now as for the work according to one ource hard work pro tect from t herea according t nother ource hard ork predispo es t it Th plus ça change plus est l m me chose

Perhaps I should add remark made by Professor D ies th connection F it does not CAUSE atheroma it aggra tes it Incidentally nonf t theroma is pparently not rare in Africans (Sev eral of the foregoing remarks by Professor Da ies are embodied in paper of his the journal *Laboratory Investigation* However he as kind enough t giv me his findings ahead of time)

I hope that these few lines will help t confuse your readers as they keep me confused But ex tenebris lux

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To the Editor

W ha read the annotation The Blight of Medical Science by Hans H Hecht (*American Heart Journal* 61 82 1961) w th considerable inter est understanding and sympathy Wh le perhap not in complet agreement w th the proposal w feel that short nnotation by such acknowledged medical thinker is timely and well orth of pub lication

W ha awakened from our philosophic reverie by the annotation by Dr Mendlowitz which fol lowed While purporting t describe the Bruit de Roger the annotation concerns itself with hemo dynamically significant entricular septal defects nd a good deal of the space is devoted to information on pulmonary stenosis and trial septal defect The concluding sentence— Today these clinical surmises can be confirmed or denied by the catheter and ...

the operating room—implies that clinical evaluation of patients with heart disease has remained stationary since Roger's time. Much has been written in the past few years on clinical diagnosis in heart disease by experts in this field, pointing out the accuracy with which diagnosis can be made with eyes, hand, and stethoscope. We believe that the catheter and the operating room have provided the stimulus making such clinical advances possible, that more accurate knowledge concerning auscultation has accumulated in the past 15 years than in the preceding half century, and finally, that a realistic appreciation of the information to be gained by clinical examination should have been included in this annotation.

Dr. H. Hecht deplores the volume of scientific literary effusion in which we are all being swamped. The implication is clearly that far too much is published which does not merit publication. We would agree with many of his sections and suggest—in retrospect—that the annotation on the Bruit de Roger could well have been omitted without detracting from the value of the *American Heart Journal*.

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To the Editor:

An annotation is meant to be provocative rather than provoking, but in this instance it has apparently been both. It also does not necessarily incorporate reviews of the literature, and if some recent efforts of the writers of this letter or of papers to which they refer have not been mentioned, I do not think that any apology is necessary.

It is always popular to praise the accuracy of the hand, eyes, ears, and stethoscope because these members and that instrument are usually available to all physicians. It therefore fortifies the ego of the clinician to decry gadgetry except as it confirms clinical experience or refines clinical interpretation. Nothing that I wrote, however, in my opinion impugns the promises of clinical medicine or implies that effort should not be made to improve the interpretation of clinical auscultation.

I merely contend that when confronted with a systolic murmur loudest in the left parasternal region in the third intercostal space, it is not always possible to be certain of the underlying congenital lesion by auscultation. At least this has been in accord with my clinical experience *despite efforts to* improve my acumen from reading of the experience of others, including that of my Canadian colleagues. Surely they do not propose subjecting such a patient to surgical intervention on the basis of auscultatory and routine clinical findings alone.

There is another aspect of this letter which I believe *requires some comment. The writers criticize* the Editor of the *American Heart Journal*, which is their privilege, for accepting my annotation, but soften the blow by praising that of Dr. Hecht, an acknowledged medical thinker. The contrast thus implies that I am neither acknowledged nor a thinker. I presume that they would not go so far as to deny the *medical*. This, however, does not disturb me very much because it occurs to me that the lack of acknowledgment is largely on the part of the writers. I agree with them, however, in their estimate of Dr. Hecht.

I cannot, however, agree with what Dr. Hecht says in his annotation and therefore must also disagree with the writers on this count. It seems to me that as the volume of scientific effort grows, the *medical* literature *must perforce* become larger. I would like to see more rather than fewer original papers published. The great advances in medicine are the result of joint effort and not an extension of some individual ego. I prefer fresh original work to the warmed over potpourri of the review. How, for example, would Dr. Hecht react if his timely, delightful, and thought *provoking paper on* Brisket Disease were ignored by some reviewer who perhaps considered it of little clinical significance or worse disagreed with the conclusions.

There was a time when a physician could keep abreast of all the medical literature. Today he can hardly do this in cardiology, and the time will come, if it has not already come, when at least I will not be able to keep up with the advances in auscultation. I wish the writers of this letter better luck but do not think that this need warrant suppression of medical literature and therefore to some extent of scientific effort.

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Book reviews

NIERENKRANKHEITEN. By Prof. Dr. François Reubi, Professor für innere Medizin u. 3. Direktor der Medizinischen Universität Poliklinik, Bern, Switzerland. Bern and Stuttgart, 1960, Verlag Hans Huber. 758 pages, 173 illustrations. Price DM 88.

This new monograph on diseases of the kidney, and although published first in German, it was written in French and then translated by two of the author's colleagues. For English-speaking readers the resulting text is probably easier to read than most books in the German language.

In the first 125 pages there are brief accounts of anatomy and physiology and a good presentation of renal function tests, including the estimation of renal blood flow and glomerular filtration rate. These latter are evidently used more frequently by Reubi in daily hospital practice than by most, and receive proportionately greater emphasis throughout the sections of the monograph dealing with individual diseases. Whatever one may think about their routine use, it is good to have a summary of what can and cannot be expected of clearance determinations by an exponent who has applied them extensively. The superiority of the 15 minute collection in the performance of the P.S.P. test is recognized, but the direction to be the patient empty the bladder before the injection of dye continues to be given in spite of the advantage which a large specimen affords in reducing the error due to residual urine.

The major part of the book is divided into sections dealing with (1) glomerular diseases, (2) tubular and interstitial diseases including pyelonephritis and the shock kidney, (3) vascular nephropathies, (4) functional disturbances. Two final chapters are concerned with the treatment of acute and chronic renal insufficiency. The classification used is similar to that of Allen. Each disease is discussed systematically with frequent emphasis on pathophysiology, and significant points are often illustrated with pertinent case histories. There are the numerous illustrations of renal biopsies which unfortunately are often not reproduced well enough to be truly helpful. Useful space for other diseases is happily preserved by keeping the discussion of essential hypertension within reasonable limits, occupying only 77 pages.

The discussion of pyelonephritis, Reubi does not mention quantitative bacteriology of the urine nor (because of its simplicity, greater omission) the importance of stained smears of freshly collected urine. He has recognized the occurrence of phenomenal in pyelonephritis but was unaware of its having been found earlier by Tracy B. Mallory. The important contribution of Kimmelstiel-Smith and associates on the pathology of malignant hypertension was apparently overlooked.

Professor Reubi's book is quite comprehensive, and it is difficult to recall any significant disorders which have not been adequately discussed. Its wide scope and predominantly clinical emphasis combine to give it a character which is not matched by any recent monograph in the English language, and it is recommended to physicians who read German.

CLINICAL CARDIOPULMONARY PHYSIOLOGY. Edited by Burgess L. Gordon, M.D. (92 contributors). Sponsored by the American College of Chest Physicians. Second edition. New York, 1960, Grune & Stratton, Inc. 1,001 pages, 778 illustrations. Price $25.50.

A comprehensive presentation of the entire field of cardiopulmonary physiology would be an enormous task. An attempt to accomplish that in this volume has resulted in a collection of 1,001 pages contributed to by 92 different authors, many outstanding authorities in their field.

The material is presented in 63 chapters divided into 12 large sections. These sections are as follows: I. Cardiac Physiology—General Considerations; II. Evaluation of Cardiovascular Physiology; III. Physiologic Aspects of Cardiovascular Diseases; IV. Associated Functions of the Heart and Lungs; V. Pulmonary Physiology—General Considerations; VI. Evaluation of Pulmonary Physiology; VII. Restrictive Diseases of the Chest; VIII. Obstructive Diseases of the Chest; IX. Chest Diseases With Both Obstructive and Restrictive Components; X. Physiologic Therapy of Pulmonary Diseases; XI. Diseases of the Mediastinum; XII. The Relation of Special Environmental Influences to Cardiopulmonary Physiology. In the volume 318 pages are devoted to cardiovascular structure, physiology, and disease; 80 pages to associated functions of the heart and lungs; 439 pages to pulmonary structure, physiology, and disease; 19 pages to mediastinal disease; and 66 pages to special environmental influences on cardiopulmonary physiology.

This type of volume by many authors covering many topics is extremely difficult to review critically. To point out several items of more controversial or omissions hardly worth while. Only general comment and a few illustrative points can be given. The presence of a few excellent and outstanding contributions does not justify praise for the whole work. Also a few poor sections do not detract heavily from the over-all basic value of the volume. It is not feasible to comment on each of the 63 chapters or even to list them by titles in this review.

To decide exactly the requirement of readers that are directed is difficult. Certainly, however, here are methods of value here for all members of the medical field. For the general practitioner much could be gained, but the coverage is possibly too time-consuming. For the cardiologist inadequate space is given to certain areas, which makes coverage in his specialty far from comprehensive. He should gain much, however, from the sections which deal with pulmonary disease and physiology. Contrariwise, the

chest physician should find the ections on cardio ascular physiology and d ease qu t useful Per hap the greate t over ll alues could be derived for the physiologically oriented general nternist and thoracic surgeon

From the cardiological iew few pecific point bear mention One might expect to find in this olume more thorough coverage of basic principles of electrocardiography and ectorcard ograph Only total of 16 pages is devoted to both of these subject This seems disproportion te in comparison t 26 pages on phonocardiog raphy and 14 pages on cinecardioangiography I a ol me such thi one might expect t find emphasis on pathophysiologic mechanisms yet explanations of such phenomen as pul us para doxus pulsus alternans gallop rhythms auscults tory gap et are inadequat Only 7 pages are allotted t chapter on h perten ion and over half of this deals with therapy A chapter is de oted to resuscitation yet little mention is made of closed chest resuscitati procedures One ch pter deals w th peripheral cul r physiology but thi is incomplete and contain little infor mation on peripheral ascular di ease This re iewer feel that the olume would be much more useful if bjects not adequately covered (g therapy of many disea states) had been omitted entirely and the resulting space had been allotted t an expanded coverage of pathophy iologic m chanisms

I general each of the chapters presented supported by key references t the literature This is aluable asset and as such helps support this olume as a reference work A reference work however a gross deficiency lies in the index in which the listings t specific items covered the text are somewhat inadequate

In summary regardless of the foregoing crit ci ms this is aluable work Although occasion lly incomplete in depth t t in scope and t serves as convenient review of this major field of medicine Some of the contributions are truly outstanding for the space allotted I general the olume is clearly written The paper printing and illustrations are of excellent quality

FUNDAMENTALS OF CHEST ROENTGENOLOGY By Benjamin Felson M D Professor and Director Department of Radiology University of Cincinnati College of Medicine Cincinnati Ohio Director Departments of Radiology Cincinnati General Children Daniel Drake Dunham Christian R Holmes and Longview Hospital Special Consulta t U S P H S and Con ultant t the Dayton and Cincinnati Veterans Administration Hospital Philadelphia 1960 W B Saunders Company 301 pages 450 illustrations on 238 figures Price $10

This work expresses the knowledge and personality of an outstanding radiologist who has made important *contributions* to the roentgenology of the chest His ob ervations have been published over the ears in arious journal devoted to x ray and the chest In this olume many of them re collected and a systematic pproach t the roentgen examination of the chest is outlined N attempt is made to describe all of the diseases of the chest or ll of the thoracic aspects of systemic diseases since this has been successfully ccom pli hed other textbooks Instead after dealing with the essential of fluoroscopy nd ill trating the use of the arious projections nd special method in che t roentgenography the uthor goes on t discuss the terpretation of che t ray films in terms of the anatomic elements seen on the films He considers separately the lobes the segment the hili sels and lymph nodes the pleur the extrapleural space and diaphragm H gives special ttention to the localization of intrathoracic lesions emphasizing the silhouette sign which he has popularized and the ir bronchogram A umber of other special chest ray signs are presented in a later chapter

This book will be of great alue for all tho e intere ted the diagnosis of disease withi the chest This includes the radiologi t the specialist i pulmonary disea the cardiologist the surgeon and the general physician The cardiologi t will find the following features of special terest the book offers a ery clear statement concerning many of the pulmonary lesions associated w th heart di ease the changes which occur w th the lungs along the borders of the heart and the great essels are well illustrated an extended di cus ion of the ppearances of the pulmonary arteries nd eins and the changes in their appearance the course of cardiac and other diseases is presented the lim ts of interpretation concerning ppear ances of pulmonary arteries and eins re well draw The significance of peculia shadow such as the density sometimes seen behind the right heart explained t is reflection of the pleura t point wher the pulmonary eins come together

This excellent monograph is peppered w th instances of the author well known w t—a dded dividend to this fine contribution to the understanding of intrathoracic diseases

BLOOD FLOW IN ARTERIES By Donald A M Donald M A D M (Oxon) D Sc (Lond) Reader Physiology in the University of London t the Medical College of St Bartholomew Hospital London England London 1960 W & J Mackay & Co Ltd Baltimore W lliam & Wilkins Co 328 pages Price $8 50

This monograph contains a hydrodynamic analysis of pulsatile flow patterns n the circulation which is viewed as system in steady st te of oscill tion This contrasts with the conventional study of pul tile pre sure changes nd the use of the Windkessel analogy of Otto Frank The latter pproach is believed by the author t ha e outgrow its usef lness

The cope and fla or of this book are indicated by the table of contents which lists chapters dealing w th the nature of flow a liq id characteristics of blood flow the circulation disturbances in blood flow due to the configura

tion of the vascular bed pressure-flow relationship of oscillatory flow measurement of phasic flow velocity pulsatile flow pattern in arteries physical properties of the arterial wall pulsatile flow in elastic tube wave reflection design of manometers shape of the pressure pulse wave and the estimation of cardiac output from pressure recordings Each topic is treated concisely and critically The author clearly develops and supports his own points of view Experimental limitations and difficulties as well as areas of ignorance are clearly pointed out

This book should be most useful to the physiologist who wishes a thorough survey of this particular area The physiologically oriented clinician may be frightened away by the plethora of mathematical formulae and by the technical nature of much of the discussion If he gets into this work he will find that the text is understandable and profitable He may suspect the author of pleasurably flexing his technical muscles at times occasionally losing sight of the topic or goal at hand Although the author regards this approach as the most promising one for the future there are no revelations for the physician beset by the problems of hypertension or arterial obstruction

The style and format are in tradition expected from the best British publications on physiology This book can be enthusiastically recommended to the audience for which it is intended—the physiologists of the present and future

Differentialdiagnose innerer Krankheiten (Differential Diagnosis of Internal Disease) By Prof Dr Robert Hegglin Professor für innere Medizin Universität Zurich Zurich Switzerland Direktor der Medizinischen Universitäts-Poliklinik Seventh revised edition Stuttgart 1960 Georg Thieme 913 pages Price DM 79 50 (In the U S A and Canada Intercontinental Medical Book Corp New York)

In the preface to the first edition published in 195 Hegglin points out two items which he hopes will give special value to his book that the pronouncement of general principles and general lines of orientation may fully compensate for the lack of knowledge in some special details and that the method of description may give an easier view for students and practitioners The further revised versions within seven years have shown that this target has been reached in every respect As far as possible the grouping of the diseases has been arranged according to pathophysiologic ideas

The details of description are general aspects anemias hemorrhagic diathesis febrile states headache dyspnea arrhythmias electrocardiographic changes cyanosis thoracic pain hypertension hypotension pulmonary infiltrations hilar enlargements enlarged lymph nodes lymphoma abdominal pain diarrhea obstipation jaundice splenomegaly hematuria proteinuria pyuria cylindruria edema pains in arms legs and spine paralyses of the motor system unconsciousness and disturbance of water and electrolyte balance as well as pH equilibration

This book gives the best confirmation for the author's point of view that only through a total synthesis of all information gained from the study of patients is the possibility for rational medical action gained In this capacity the study of Hegglin's Differentialdiagnose can be readily recommended to the specialist For instance for the cardiologist it is most exciting and worthwhile to read the author's ideas concerning the numerous relationships of cardiovascular diseases to diseases of other organ systems.

Before the preface to the seventh edition the author has placed the sentence The secret of modern internal medicine is based on the conception and coordination of the efforts of its specialists This difficult task has been fully realized by Hegglin The dedication of the seventh edition to K Jaspers as the mentor for medical unity should give an impulse to all to remember this goal

Die Behandlung der Angina pectoris mit Tersavid und anderen Monoaminoxydasehemmern (Treatment of Angina Pectoris With Tersavid and Other Monoamine Oxidase Inhibitors) Supplement 11 to Volume 37 of *Cardiologia* Basel 1960 S Karger 288 pages 51 illustrations Available in U S A through Albert J Phiebig P O Box 35 White Plains N Y Price $10 60

The papers read at Lugano in October 1959 at a meeting of pharmacologists toxicologists and physicians to discuss the treatment of angina pectoris with Tersavid and other monoamine oxidase inhibitors are reported in this supplement to *Cardiologia*

The theoretical aspects of the use of monoamine oxidase inhibitors and the clinical experiences with these agents in angina pectoris are reported However most of the experiments reported preliminary data and the clinical experiences of most investigators were based on a relatively small series of patients The point is well made that the clinical use of the so-called monoamine oxidase inhibitors has preceded adequate biochemical and pharmacologic knowledge of the actions of these agents It is stated that the clinician has had to point the way for the basic investigations of these agents Whether this is necessarily good remains to be seen A second point of consideration is the lack of a substantial number of long term experimental studies The use of reserpine and now the use of MAO inhibitors has pointed to the need for experiments designed to study the long term effects of drugs at least 3 to 6 months Often the effects seen on the second or third day in the pretreated animal are quite different from the immediate effect This point should indicate that the pharmacologic basis for the use of these agents will require considerable investigation time

In the section on theoretical aspects an attempt

is made t relate the biochemical and pharma ologic effects of this group of substances to their clinical action n ngina pectoris Several hy pothe es concerning the action mechanism are advanced An increase in the blood lev l of 5 h droxytryptamine w th a reduction coro nary resistance and ugmentation of coronary flow w thout increa ed oxygen consumption in the left entricle was reported The levels of caterbolamines m myocardi l tissue were in creased and the suggestion is made that the MAO inhibitors could suppress the ischemic effect of these amines Alterations cardiac metabolism which indicat reduction in the oxygen re quirements or a more economical use of oxygen are suggested Blockade of neurohumoral tra mis ion which causes an increase in the threshold t sympathetic stimulation and a reduced pain conduction also proposed Possible participa tion of diamine oxidase inhibition was suggested Over ear after this symposium w still lack much essential knowledge bout the biochemical and pharmacologic effects of these agents It seems sad to this investigator that the name *MAO inhibitors* has been given these agent since they ha many other effects that seem t be un related t this property

The clinical aspects of the of the agents is adequately discussed by H I R sek It is pointed out that although these agents will produce symptomatic relief of the pain of angina pectori no improvement is seen in the ECG change w th exercise in these patients The com pounds do not improv the ratio of oxygen supply to demand The lack of improvement the ECG changes with exercise observed by Russek was supported by Dighiero and co workers These tw investigations comprised the largest groups of patients ob erved by one team of investigators A total of 594 cases were reported by the 14 physicia groups Approximately tw third of the patient were reported to ha e a reduction in the frequency and intensity of anginal pain

Tersa id was found t be less toxic tha M rsilid on milligram for milligram basis however Tersavid is less effectiv tha the proto type Marsilid The recommended nitial dose ppears to be bet een 150 nd 300 mg per day Maintenance dosage was about 100 mg per day The drug generally starts t take effect withi the first week of treatment but some cases require a greater period prior to the onset of action

A fair review of the literature in regard to the actions of these agents at the time of the sym posium included The book is recommended to investigators interested in these gents

Announcements

The Eleventh Annual Instrument S mposium and Rese rch Equipment Exhibit will be held t the N tional Institutes of Health Bethesda Md Oct 9 through Oct 12 1961

Instrument Symposium Committee on Sympo sium on Recent Developments Re earch Methods and Instrumentation Chairman Dr Julius Sen droy J Na al Medical Re earch Institute Be thesda Md Executiv Secretary M James B Da is National I titutes of Health

The primary topics for discussion on the scientific program include (1) Applied Gas Chromatograph (2) Factors Influencing I terpretation f Spectra (3) Electron Magnetic Resonance (4) Thermogra metric Analysi (5) Electron Probe Analysis (6) Application of Physiological Instrumentation to Clinical Problems and (7) Optical Rotatory Dis persion

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The Council on Scientific Assembly of the American Medical Association invites physicians t submit titles and brief bstracts of cientific papers that they wish to deliver t the 1962 annual meeting of the American Medic l Association whi h will be held in Chicago June 11 15 1962 The dead line Oct 15 1961

W would like t receiv as many titles and bstracts as possible said Council Chairma Samuel P Newman of Denver because in that w y w hav better selection and this in turn assures a mor timely nd better scientific program

The American Medical Association meeting in 1962 will be held in Chicago new $35 000 000 expo sition center on Lake Michigan which has 300 000 square feet of exhibit space al one

Physicians who wish to participat in the Chicago scient fic program and desire information are in vited t writ to Dr Charle Bramlitt Secretary Council on Scientific A sembly America Medical Association 535 North Dearborn St Chicago 10 Ill or to any council member

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Editorial

Bradykinin

Egon Sturmer M D
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Basle Switzerland

We still know very little about the physiologic and pathophysiologic significance of bradykinin (Br) It is an endogenous polypeptide possessing great biologic activity and synthesis in the Sandoz laboratories in May 1960 has fully elucidated its chemical structure Unlimited amounts of the pure substance are thus available for further investigation

Isolation elucidation of structural formula and synthesis are traditional hurdles in the path that leads to a more profound knowledge of endogenous substances In the case of Br these obstacles have now been overcome and investigations with Br can be expected to be intensified It is fitting therefore at this moment to review the present state of affairs in this area of research

I Discovery isolation and elucidation of the structure In November 1948 Rocha e Silva Beraldo and Rosenfeld described a new active biogenic substance which caused slow contraction of isolated intestine Because of this property they named the new substance *bradykinin* (*βραδύς* = slow *κινεῖν* = to move) The behavior of Br led them to conclude that it possessed a polypeptide structure By 1956 much progress had been made in the purification of B through the use of chromatographic and ion exchange techniques However it was not until 1959 that an English team employing a combination of chromatography and electrophoresis succeeded in isolating the pure substance from a crude material obtained by the action of crystalline trypsin on ox pseudoglobulin In April 1960 the English workers proposed[4] the following structure Arg Pro Pro Gly Phe Ser Phe Arg (I) Synthesis of this compound in the Sandoz laboratories[5] yielded a product which was devoid of activity [6,7] This was confirmed by other investigators [8]

Planned synthesis of variants of (I) yielded Arg Pro Gly Phe Ser Pro Phe Arg (II) an octapeptide which had some Br activity In view of this Boissonnas Guttmann and Jaquenoud decided to introduce a further proline residue into the molecule In this way they arrived at a nonapeptide Arg Pro Pro Gly Phe Ser Pro Phe Arg (III) which in its biologic chemical biochemical and biophysical properties could not be distinguished from natural Br [7, 14] Since the biologic properties of all known polypeptides depend in a highly specific manner upon their chemical structure nonapeptide III must be either closely related to or identical with natural Br It has since been confirmed that the two are in fact identical [14]

F[illegible] th Ph[illegible] [illegible]ol gical Labora[illegible]ry Sa[illegible]d[illegible] Ba[illegible]l[illegible] Switzerland
Rec[illegible] f[illegible] [illegible] F[illegible] 196[illegible]

The synthesis of a complex endogenous substance before its structure has been fully elucidated must surely be a rare event in the history of biologic chemistry.

An exact comparison has still to be made between the chemical structure of trypsin Br and Br produced by the action of snake venom on plasma.[1] From the biologic evidence, however, the two forms should prove to be the same.[16,17]

II. Liberation of bradykinin. Br is liberated from a precursor, *bradykininogen*, which is a normal component of the pseudo-globulin fraction of the plasma. Both snake venom and trypsin have a powerful proteolytic action and it therefore seemed reasonable to suppose that Br might be produced by peptide cleavage. However, the evidence suggests that Br is liberated from bradykininogen by cleavage of an ester linkage.[8] The details of the process whereby Br is set free in the living organism under physiologic and pathologic conditions have still to be clarified.[21] One thing is certain, however: practically every cell in the body possesses proteolytic and esterolytic enzymes and has at its disposal the substrate bradykininogen, which is a normal constitutent of plasma and lymph.

III. Pharmacology of bradykinin. Studies have shown that pure Br is one of the most active substances found in the body. Four principal actions have been distinguished: (1) an effect on smooth muscle in vitro and in vivo, (2) an effect on blood vessels or circulation, (3) an effect on capillary permeability, (4) local effects on tissues eliciting edema, migration of leukocytes, and pain.

The response of isolated guinea pig ileum to Br differs from the response to histamine and acetylcholine. Br evokes a slow contraction dependent on the dose with a latent period of 25 to 50 seconds. The threshold dose is 1 ng/ml (1 ng = 0.001 µg). Weight for weight, Br is as active as histamine.[7]

In isolated organs with spontaneous motility, Br first causes relaxation, which is followed by a contraction.[7,22]

By far the greatest sensitivity to Br is displayed by the isolated rat uterus, which responds to a dose of only *0.03 ng/ml*. Br is almost as active as oxytocin in this preparation.[7,22]

In guinea pigs and spinal cats, Br, when administered by the intravenous route, elicits bronchoconstriction.[7,23,24]

Intravenous administration of 0.05 to 0.5 µg/kg of Br produces a fall in blood pressure in all mammals so far investigated (rat, guinea pig, rabbit, cat, and dog). In the guinea pig, rabbit, and dog the vasodepressor activity of Br is greater than that of acetylcholine.[7]

Br by intracutaneous injection increases *capillary permeability to circulating dyes* of high molecular weight.[7,23,24] A dose of 1 ng/0.1 ml elicits a clear effect. In this experiment, Br is 10 to 15 times more active than histamine.

Local application of Br causes edema and pain, classic signs of inflammation.

Injection of Br in the rat paw elicits edema which can readily be measured.[24] In this test Br is about 10 times more active than histamine, weight for weight.

Intradermal injection of Br in a concentration of 10^{-7} in the guinea pig has been found to lead to an accumulation of leukocytes at the site of injection and migration in the surrounding tissues.[21]

If a blister produced by cantharidin is opened and Br applied to the blister base, pain is experienced. The threshold concentration is 10^{-7}. The pain is transient and decreases on repeated application (tachyphylaxis?).[22]

Doses which elicit acute *toxicity* by the intravenous route are large compared with doses required to produce a response. The LD_{50} intravenously for white mice is between 16 and 20 mg/kg. Five rats with body weights between 150 and 160 grams survived the intravenous injection of 10 mg/kg of Br. A dose of 3 mg/kg administered to a dog intravenously within 10 seconds did not prove fatal, although respiration was temporarily arrested and severe transient disturbance of gastrointestinal function was observed.[7]

Intravenous infusion of Br (2 to 50 µg/kg/minute) in cats caused an initial steep fall in blood pressure. Subsequently, the blood pressure rose to stable but still subnormal levels which depended upon the rate of infusion. Doses of up to 1.85 *mg/kg* given over 4 hours did not produce any sign of intoxication.

Investigations to determine the influence

of drugs on the effects of Br have been undertaken with impure Br but not so far with pure Br.

Rocha e Silva, Corrado and Ramos[8] investigated whether vasodepressor drugs were able to modify the action of Br. They found that hexamethonium did not affect the fall in blood pressure elicited by Br whereas dibenzylin, chlorpromazine and reserpine enhanced and prolonged it. Cocaine attenuated the effect of Br.

Collier, Holgate, Schachter and Shorley[72, 4] investigated the effect of a number of substances on Br bronchospasm. The most potent inhibitors were acetylsalicylic acid, phenylbutazone, amidopyrine and phenazone. Pretreatment with cortisone had no influence.

Lecomte and Troquet[39] have reported that high doses of phenylbutazone (100 mg./Kg.) will block Br vasodepression in rabbits.

The search for substances which inhibit the various effects of Br is of twofold importance. It should contribute to our knowledge of the mechanisms of action of Br and it may yield information of practical therapeutic value.

IV. Physiology and physiopathology of bradykinin. We know little as yet about the physiology and physiopathology of Br, but what data we have indicate that Br or closely related peptides (plasma kinins) play a highly important role in the organism.

Research on the kinins has already completed the picture in one area of physiology, namely, the theory of cholinergic vasodilation in glands. Atropine does not, as would be expected, suppress vasodilation in the submaxillary gland in response to stimulation of the chorda tympani. It was demonstrated that during periods of activity the gland releases an enzyme which in turn liberates a vasodilator substance from plasma.[50, 51] This substance cannot be distinguished from Br. Thus, the circulation in the gland is under local humoral control. The enzyme which liberates Br is probably the same as kallikrein, an enzyme discovered by Werle[53] in the saliva. It must be assumed that this local humoral mechanism which controls the blood supply to the submaxillary gland is a feature common to other secretory organs, for the same enzyme has been shown to occur in the secretory areas of the tongue,[54] in the pancreas,[57] in lachrymal secretion[58] and in the sweat glands.[33]

Whether the blood supply of striated muscle is under similar humoral control has still to be elucidated. At all events, Br has not so far been detected in the venous outflow of working muscle.[34]

Pure trypsin Br administered to cats by injection in skin and muscle arteries produces vasodilation. The potency of Br is roughly equal to that of acetylcholine.[40] Plethysmographic studies in man have revealed that intra-arterial injection of Br produces a considerable increase in blood flow.[41] Injection of 1 μg. of Br is always followed by increased blood flow. In one experiment an increase of from 5 to 33 ml./100 grams of tissue per minute was observed. Br is as active or rather more active than histamine and approximately 10 to 100 times more active than acetylcholine.

The role of the release of Br in pathologic conditions is still obscure. It is reasonable to suppose that liberation of Br occurs in the case of trauma, inflammatory reactions, cardiac infarction, and states of shock. The following scheme of events is possible.

The first reaction to trauma is the liberation of histamine,[42] which, by increasing capillary permeability, might allow the intracellular enzyme responsible for the liberation of Br to escape. Possibly the so-called H-colloid[43] is identical with Br or the enzyme which produces it.

Increased protease or fibrinolytic activity has been described in a number of conditions: in inflammatory reactions,[44, 45] after operations,[44, 47] in anoxemia,[44] burns, hemorrhage,[49] anaphylactic shock,[49] and barbiturate poisoning.[47] It is conceivable and compatible with the clinical symptoms that generalized liberation of Br might occur during this unspecific reaction. The vasodilation that occurs in insulin shock has also been ascribed to the liberation of vasoactive peptides.[51] However, no relation has been demonstrated between the plasma level of Br and the symptoms in peptone shock and anaphylactic shock artificially induced in laboratory animals.

Much work will be needed to assess the importance of Br as a mediator in inflammatory reactions.

I *Unidentified kinins with properties similar to those of Br* Chapman and Wolff[14] incubated ox globulin with cerebrospinal fluid from migraine patients undergoing an attack chronic schizophrenics patients with acute cerebral damage and patients with persistent pain as a sequel to pelvic or leg operations In this way they found a substance similar in behavior to Br More recently a substance resembling Br which has been given the name *neurokinin*[10] as well as a neurokinin forming enzyme have been detected in the subcutaneous tissue of migraine patients during the attack In view of its bradykinin like properties neurokinin would be well able to give rise to some of the clinical symptoms of migraine namely vasodilation cutaneous edema and pain Interestingly enough the level of neurokinin falls to that of normal controls after administration of ergotamine tartrate this coincides with the onset of therapeutic action and a decrease in the intensity of the headache

In lung perfusion experiments on sensitized guinea pigs Brocklehurst[18] demonstrated the presence of a slow reacting smooth muscle stimulating substance (SRS A) in the perfusate after addition of the antigen This substance may be related to Br It is of interest to note that in perfusion experiments with lungs resected from asthmatic patients SRS A has been detected when pollen antigens were added o the perfusate

Armstrong Jepson Keele and Steward[7] have described a pain producing substance (PPS) which is possibly related to Br It is formed when plasma comes into contact with glass surfaces The substance elicits pain when applied to a blister base and stimulates the isolated uterus to contract It is possible that PPS is released in vivo in trauma and in antigen antibody reactions (at the surface of the antigen antibody complex)

A further kinin has been isolated from the urine[14,23] The amount excreted calculated on an activity basis with respect to pure Br varies between 10 and 30 μg per 24 hours[60] It may be that this substance is excreted in the urine in the normal course of clearance of kinin from the plasma Alternatively it could be a kinin that is produced locally in the kidneys and that has an influence on renal blood flow

Werle and co workers[61] have detected an enzyme in urine pancreatic juice and saliva The enzyme kallikrein liberates a polypeptide kallidin from alpha 2 globulin This polypeptide cannot be distinguished from Br[4,62]

The migration of leukocytes that is observed after an injection of Br suggests that the polypeptides described by Menkin[63,64] might be identical with or related to Br Wasp venom contains a kinin which closely resembles Br in its pharmacologic properties However this substance can be separated from Br and kallidin by chromatographic methods[65,67]

Br is one of the most potent substances found in the organism but beyond this little is known about its physiologic functions or possible roles in pathophysiologic states Whether the various kinins which have been described are identical with Br is still uncertain

At present it appears that Br might play a part in the regulation of blood supply in certain glands and that it might be implicated in shock inflammation asthma rheumatic disease migraine painful states and chronic schizophrenia The actions of Br must be further elucidated and it is desirable to find antagonists to these actions

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Clinical communications

Studies of hypothermia in ventricular tachycardia after myocardial infarction

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Ventricular tachycardia after myocardial infarction has a grave prognosis.[1,2] Among the contributing factors are low cardiac output, poor coronary perfusion, and frequent refractoriness of the arrhythmia to therapy.

Hypothermia has certain effects which might be beneficial in the case of ventricular tachycardia. The ratio of coronary blood flow to cardiac oxygen consumption is increased with cooling,[4] peripheral metabolic demands upon the heart decline, and mechanical efficiency increases.[4] The decrease in cardiac rate associated with hypothermia is an additional benefit, since tachycardia contributes to poor cardiac output and low coronary perfusion.

A major risk of hypothermia in normal animals is the tendency of the cooled heart to develop ventricular fibrillation, particularly at temperatures below 25° C.[5] The potential supportive benefits of hypothermia in ventricular tachycardia after myocardial infarction, therefore, are offset by this possible arrhythmic effect of cooling.

A series of experiments designed to study the risk of hypothermia in ventricular tachycardia after myocardial infarction is reported. These include observations of the effects of spontaneous breathing and mechanical hyperventilation and an investigation of the relative significance of hypercapnia and acidosis to the occurrence of ventricular fibrillation.

Methods

An experimental preparation for the induction of ventricular tachycardia was described by Harris.[6] This consists of a two stage ligation of the anterior descending branch of the left coronary artery in the dog. This is followed within about 12 hours by a stable ventricular tachycardia that persists for from 1 to 2 days. In this study the animals were subjected to hypothermia 24 hours after the Harris operation.

The procedure was performed on 35 mongrel dogs which ranged in weight between 8 and 20 kilograms. The animals were divided into four groups as recorded in Table I A-D. The grouping was based on whether or not the arrhythmia appeared after the operation and whether the animals were hyperventilated or allowed to breathe spontaneously. Ten animals failed to exhibit the arrhythmia (Group I). Of the other 25 dogs which developed ventricular tachycardia, 10 were cooled while breathing spontaneously (Group II), 12 were hyperventilated as they became hypothermic (Group III), and 3 were hyper

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Table IA Group I Myocardial infarction sinus rhythm spontaneous breathing

Dog number	Control			Hypothermia			Outcome
	Temp (C)	Heart rate	% Sinus beats	Temp (C)	Heart rate	% Sinus beats	
14	40 37 5	192 174	100 100	28			Died—standstill—fibrillation
16	37 37 ( )	200 155	99 92	29 26	90 90	98 100	Survived
23	38 38 ( )	155 140	95 94	29	86	99	Survived
26	36 5 37 (r)	140 205	96 100	29	130	99	Survived
29	37 38 ( )	185 159	100 100	28	64	100	Survived
31	40 5 36 5 37 ( )	168 176 173	100 100 100	29 5	83	100	Survived
32	36 5	150	93 5	29	67	100	Died—fibrillation
34	38 37 ( )	178 161	100 100	29	83	100	Survived
35	40 5 38 5 37 5 ( )	146 151 136	100 100 98 5	29	81	100	Survived
36	38 5 37 (r)	165 120	92 91 5	30	87	99	Survived

(r) Rewarmed

ventilated until a rectal temperature of 29° C was achieved after which mechanical ventilation was discontinued (Group IV)

Hypothermia was induced in 25 dogs by immersion of the entire body in ice water In the other 10 animals irrigation of the skin with alcohol was employed

Pentobarbital was administered in doses just sufficient to prevent shivering Rectal temperatures taken with a standard mercury thermometer were lowered to 26° to 30° C at which level the animals were maintained for from 1 to 5 hours Thirteen dogs were then rewarmed to normal temperatures by exposure to room air

Hyperventilation was achieved with a mechanical respirator connected to an endotracheal tube The minute volume of respiration was 6 to 9 liters per minute with the apparatus Continuous electrocardiographic monitoring was employed Heart rate and the percentage of sinus beats seen in Lead II of the electrocardiogram at different temperatures were recorded in all of the animals All electrocardiographic complexes that appeared to be of supraventricular origin were counted as sinus beats

In 10 dogs with ventricular tachycardia and in 2 normal animals comparisons were made as follows in 3 dogs with tachycardia a comparison was made between the effects of delivering gas mixtures containing 5 per cent carbon dioxide and 95 per cent oxygen and 25 per cent carbon dioxide and 75 per cent oxygen in the other animals the effects of 25 to 30 per cent carbon dioxide (70 to 75 per cent oxygen) was compared to those of intra

venous 0 1N hydrochloric acid Observations were made on the arterial pH the electrocardiogram and the survival rate The Beckman pH meter was used for measurements of pH and the experiments were all performed during hypothermia

Results

Hypothermia was induced in dogs in which ligation of the coronary artery was not followed by ventricular tachycardia Of 10 animals with infarction alone (Group I) 2 died during cooling In this group a slowing *of heart rate from 10 to 70 per* cent (average 50 per cent) was observed The percentage of sinus beats which ranged between 90 and 100 per cent was not significantly altered by cooling These dogs were not hyperventilated The results for Groups I IV during hypothermia are shown in Table I A D

Among the spontaneously breathing dogs with both infarction and ventricular tachycardia hypothermia had an obviously detrimental effect Nine of the 10 animals in this category died 6 of which exhibited terminal fibrillation (Group II) When comparison of rates could be made cooling again exerted a bradycardiac effect in 5 animals a 50 per cent reduction in heart rate was observed The slowing effect of hypothermia upon the sinus rate has been recorded [9] A similar slowing of the ventricular pacemaker by the cooling was observed in Dogs Nos 33 and 58 predominantly ventricular rhythms persisted during hypothermia at half the control rate When *it could be measured* the percentage of sinus beats increased somewhat in 4 of 5 dogs in response to hypothermia

Of 12 dogs which exhibited myocardial infarction and ventricular tachycardia and were hyperventilated throughout cooling and rewarming *10 survived hypothermia* (Group III) The heart rate showed a 24 to 68 per cent slowing in all dogs with an average fall of 53 per cent as a result of lowering of the temperature In 4 dogs

Table IB *Group II Myocardial infarction ventricular tachycardia spontaneous breathing*

Dog number	Control			Hypothermia			Outcome
	Temp (C)	*Heart rate*	*% Sinus beats*	*Temp (C)*	*Heart rate*	*% Sinus beats*	
17	40 37 5	170 165	97 5 6 5	33			Died—standstill
21	38 5	165	1 0	30			Died—fibrillation
25	38 5	199	74	30 5			Died—fibrillation
30	40 35	179 143	55 100	29			Died—standstill
33	39 28 (r)	161 16	0 0	29	82	6	Survived
37	40 5 36	180 175	17 5 16	28	30	1	Died—fibrillation
56	37	175	42	28	144	0	Died—standstill
58	40	170	30 8	29	75	48	Died—fibrillation
60	39	183	7	27			Died—fibrillation
66	39 37	120 120	40 5 0	28	51	75	Died—fibrillation

Each [illegible] [illegible] [illegible] [illegible] [illegible] [illegible]
(r) Rewarmed

Table IC. Group III. Myocardial infarction, ventricular tachycardia, hyperventilated

Dog number	Control			Hypothermia			Outcome
	Temp. (° C.)	Heart rate	% Sinus beats	Temp. (° C.)	Heart rate	% Sinus beats	
	37	160	71	29	80	0.5	Survived
9	39	154	20	29	53	88	Survived
10	38	167	6.5	33			Died—fibrillation
18	40.5 37 37.5 (r)	191 160 175	10.5 50 24	29	103	73	Survived
19	40 38 36.5 (r)	157 145 167	60.5 90 94	29	112	95	Survived
20	40 37.5 36.5 ( )	167 158 131	77 100 100	29	82	100	Survived
28	40.5 38 38 ( )	158 145 177	1.0 0 87.4	27	67	95.1	Survived
51	38.5	165	6.8	29 26	55 45	77.2 7.1	Survived
55	34	145	0	26	75	0	Survived
59	38.5	170	9.5	27			Died—fibrillation
67	40	170	7.2	29	55	12.8	Survived
70	38	150	0	29	60	0	Survived

*Received sufficient [illegible] to maintain ventricular tachycardia.
(r) Rewarmed.

(Nos. 51, 55, 67, and 70) the slowing effect of hypothermia on the ventricular pacemaker was evident (average fall in rate of 61 per cent). In this group of animals, as in the previous two groups, hypothermia had no consistent effect upon the percentage of sinus beats.

After hypothermia was induced, discontinuance of hyperventilation proved fatal to 3 dogs (Group IV). Death occurred in these animals within 2 hours after mechanical ventilation was stopped. Hypothermia slowed the heart rate (average 52 per cent) in each dog. The inconsistent effect of cooling on the proportion of sinus beats was also evident.

Moderate fever secondary to the original operative procedure was present in some of the dogs in each of the four groups at the time that hypothermia was induced. Lowering of the temperature to normal levels usually caused a slight fall in heart rate, but no consistent effect on the percentage of sinus beats was observed.

Ten hyperventilated dogs with ventricular tachycardia which was stable during hypothermia for at least 1 hour were given either dilute hydrochloric acid intravenously or gas mixtures containing 5 to 30 per cent carbon dioxide with oxygen, or both successively, with a half hour pause between to allow arterial pH to return to normal. The results are shown in Table II. Of 7 dogs with tachycardia which received acid only 2 died; both had pH levels below 6.0. Of 7 animals which received 25 to

30 per cent carbon dioxide via the mechanical respirator 6 died between 5½ and 30 minutes after inhalation of carbon dioxide was begun The arterial pH of 7 of the dogs which received carbon dioxide was somewhat lower than the pH of the surviving dogs which were given acid intravenously (average 6 56 versus 6 84 for 5 minute pH values) Two dogs survived inhalation of 5 per cent carbon dioxide and 2 nonoperated dogs survived both infusion of acid and inhalation of 25 per cent carbon dioxide The 3 dogs which received 25 to 30 per cent carbon dioxide and did not die exhibited prolonged intraventricular conduction time and bizarre complexes

Discussion

Ventricular tachycardia induced by the Harris procedure in dogs resembles the human counterpart in the duplication of

*Table ID G oup I1 Myocardial infarction ventricular tachycardia partly ventilated**

Dog number	Control			Hypotherm			Outcome
	Temp (C)	Hea t rat	% S beat	Temp (C)	Heart rate	% S beat	
13	41 37	154 140	34 91	29 29	87 93	27 4 0	Died—fibrillation
15	40 37 5	154 160	44 2 5	29 29	7	2	Died—stand till
65	3	153	67	28 28	55	100	Died—standstill

D (a / Based count of m 1 at at 1

Table II

Dog number	Amount of acid inf d (0 1 N HCl) ( )	Arterial pH (5 m)	Result	% CO₂ given and time	Arterial pH (5 m n)	Result
43	——	——	——	5%—30 min	——	Survived
31	——	——	——	25%—11 min	——	Died
45	——	——	——	5%—20 m 25%— 8 min	—— 6 5	Surv ed D d
67	100	5 3	Died	——	——	——
63 (Normal)	90	6 85	Survived	25%—30 mi	6 30	Surv ed
70	150	6 70	Surviv d	25%—16 min	——	Sur ed
71 (Normal)	150	6 90	Survived	25%—30 m	6 70 t 30 mi	Survived
73	50 (0 2N)	5 80	D ed	——	——	——
74	100	6 83	Surv ed	30%—13 m	6 60	Died
75	75	6 95	Surv ed	30%— 6 min	6 55	Died
8	120	6 85	Surv ed	30%—30 min	6 55	Died
80	200	6 80	Survived	30%—3 min	6 60	Died

the sequence of infarction followed by arrhythmia in the hypotension that occurs with the arrhythmia and in its partial susceptibility to termination by antiarrhythmic agents [10,11] The two entities differ in that the canine arrhythmia is multifocal

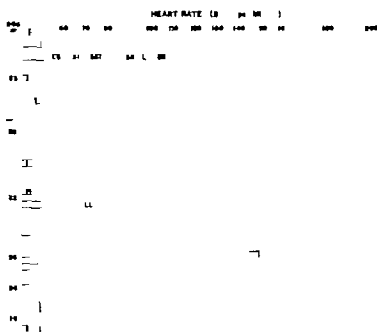


Fig. 1 Effect of hypothermia on heart rate in 10 dogs with myocardial infarction alone Strippled bars indicate normothermic temperatures and solid bars either febrile or hypothermic temperatures Eight of 10 dogs survived hypothermia followed by restoration to normal temperature

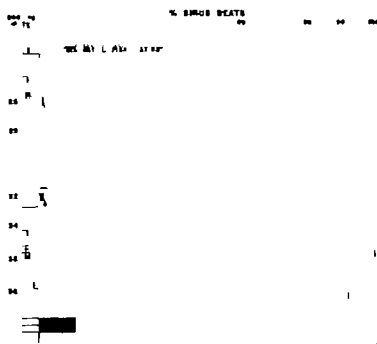


Fig 2 Effect of hypothermia on the proportion of sinus beats in 10 dogs with myocardial infarction alone

self-limiting, possesses a rate close to the sinus rate and does not often prove to be fatal if untreated.

In the experiments reported here, hypothermia carried a high risk in the case of ventricular tachycardia after occlusion of the coronary artery if the animal breathed spontaneously during cooling. If the dog was hyperventilated the risk of fibrillation was greatly reduced and was no more

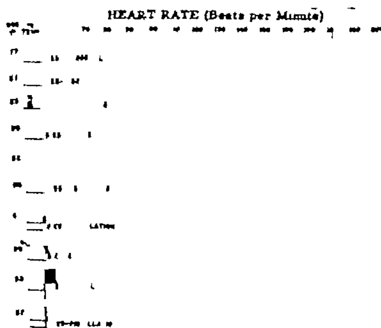


Fig. 3. Effect of hypothermia on heart rate in 10 dogs with infarction and ventricular tachycardia which were breathing spontaneously.

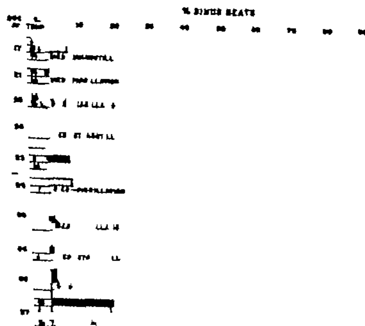
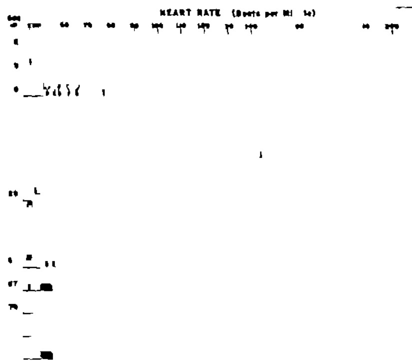


Fig. 4. Effect of hypothermia on the proportion of sinus beats in 10 dogs with infarction and ventricular tachycardia which were breathing spontaneously.



Fi, 5 Effect of hypotherm on heart rate in 10 dogs w th infarction and entri ul tachycardia which were hyperventilated throughout

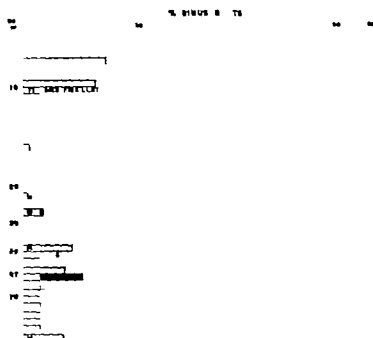


Fig 6 Effect of hypothermia on the proportion of sinus beat i 10 dogs with infarction and entricular tachycardia which were hyperventilated throughout

severe than the risk of cooling a dog with myocardial infarction in the absence of ventricular tachycardia. Cessation of hyperventilation after the animal had safely reached the hypothermic level and the temperature had stabilized resulted in the death of the animal.

The hypothermic level used in these studies (26° to 30° C.) is above the range at which normal animals tend to demonstrate ventricular fibrillation. In its susceptibility to fibrillation at higher than usual temperatures the preparation used here is a more sensitive index of the tendency of cooling to induce arrhythmic death.

The three potential causes of death in regard to impaired respiration in this preparation are hypoxia, acidosis, and hypercapnia. The marked respiratory depressant effect of hypothermia in normal animals was observed in these studies.[11] It has been observed that the admini

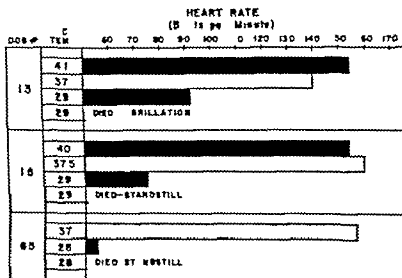


Fig. 7. Effect of discontinuance of hyperventilation. Hyperventilation maintained until the hypothermic temperature had been reached, and then the animals were allowed to breathe spontaneously. These dogs died within 2 hours after hyperventilation was stopped.

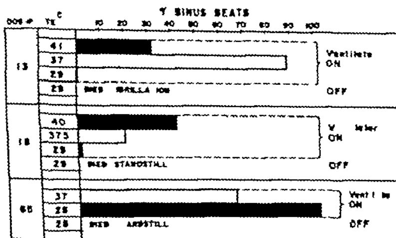


Fig. 8. Effect of discontinuance of hyperventilation. As with previous groups of dogs in this study, cooling had an inconsistent effect on the proportion of sinus beats.

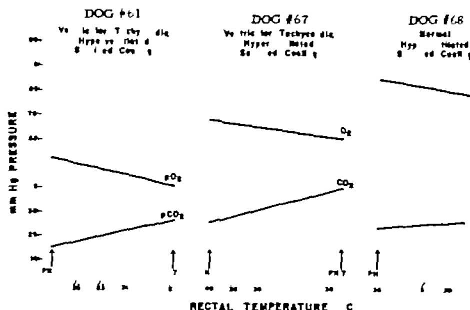


Fig. 9. Effect of hypothermia on pH, pO_2 and pCO_2 in 3 dogs which were hyperventilated throughout the period of cooling.

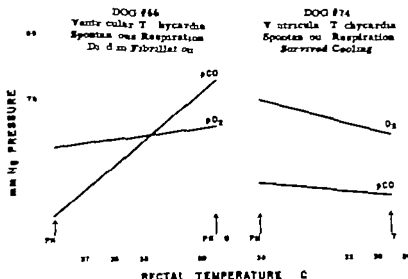


Fig. 10. Effect of hypothermia on pH, pO_2 and pCO_2 in 2 dogs which breathed spontaneously during the period of cooling.

stration of critically hypoxic gases (5 per cent oxygen or less) to normothermic dogs with myocardial infarction causes death usually by ventricular fibrillation.[12] In addition there is a current belief that acidosis is the essential element in hypothermic death.[13,4] Acidosis in association with hypercapnia is reported to increase the likelihood of ectopic discharges directly[3] and through secondary depression of extracellular potassium.[1] Hypercapnia may be of primary importance in connection with fibrillation. Discharge of catecholamine has been demonstrated in association with hypercapnia and it has been observed that rapid alterations in arterial pCO_2 levels can induce ventricular fibrillation in normal dogs.

In these studies, reduction of arterial pH levels to 6.70 for 5 minutes was not of itself fatal in the hypothermic dog with myocardial infarction and ventricular

tachycardia Although severe acidosis alone was not associated with the appearance of ventricular fibrillation it is uncertain whether or not a critical pH level exists below which death ensues or whether hypercapneic acidosis is more lethal than comparable degrees of metabolic acidosis It is possible that a critical level of pH lies between the values found after infusion of acid and inhalation of carbon dioxide Death did occur when the pH was below 6 0 after infusion of acid

These findings do not dispute the current belief that acidosis is the essential element in hypothermic death However the possible role of hypercapnia per se in causing arrhythmic death is suggested by these studies

The data presented confirm the protective value of mechanical hyperventilation during hypothermia in this preparation Hyperventilation reduced the 90 per cent risk of arrhythmic death in dogs with both myocardial infarction and ventricular tachycardia to that of animals with myocardial infarction alone (20 per cent)

Hypothermia slowed the heart rate irrespective of the site of the pacemaker In so far as part of the poor cardiac output and diminished coronary perfusion derive from the rapid heart rate of ventricular tachycardia hypothermia could be said to be helpful Hypothermia alone did not convert the arrhythmia to sinus rhythm The advantages of slowing metabolic processes within the damaged arrhythmic heart and reducing somatic demands on that heart cannot be determined from these studies

Summary

The risk of ventricular fibrillation was evaluated in dogs with ventricular tachycardia after myocardial infarction when the animals were exposed to hypothermia (26° to 30 C rectal temperature)

Eight of 10 dogs with infarction but without ventricular tachycardia survived cooling Of 10 animals with both infarction and arrhythmia only 1 survived hypothermia while breathing spontaneously Three dogs with infarction and arrhythmia survived cooling while hyperventilated but died when hyperventilation was discontinued Of 12 dogs with infarction and ventricular tachycardia which were hyperventilated throughout cooling 10 survived

Five dogs with ventricular tachycardia survived infusion of hydrochloric acid which lowered the arterial pH to 6 84 (mean) but a drop in pH below 6 0 proved fatal to 2 dogs Reduction of the pH to 6 53 with inhalation of 25 to 30 per cent carbon dioxide was fatal to 5 of 6 dogs with ventricular tachycardia

Hypothermia slowed the heart rate irrespective of the origin of the heart beat but had no antiarrhythmic effect in this preparation

These studies support the concept that hyperventilation protects against the occurrence of ventricular fibrillation during hypothermia in ventricular tachycardia after myocardial infarction It is suggested that hyperventilation probably opposes the hypercapneic acidosis associated with cooling

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Correlation of ECG, VCG, and pathologic findings in subendocardial infarcts and infarct-like lesions experimentally produced by administration of substances of high molecular weight

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Autopsy findings in patients with coronary arteriosclerosis frequently reveal spotty myocardial fibrosis or small intramural scars in the heart muscle, especially in the subendocardial layer. Some of the scars can be seen macroscopically. In other instances they can be found only by microscopic examination. These changes can be called infarct-like lesions. These changes and the large solid subendocardial and transmural infarcts have been produced in the animal heart experimentally.

It is generally accepted that the small scars are more significant than the occurrence of transient reversible myocardial ischemia. The electrocardiographic changes produced by these two conditions are the same, namely, primary changes in the S-T segment and in the T wave. Even for large solid subendocardial infarction, some authors[1-4] have pointed out that the changes in the QRS complex are seldom diagnostic, ascribing more importance to the primary changes in the S-T segment and the T wave.

Thus, these three conditions are difficult to differentiate on the basis of the electrocardiographic findings. The usual clinical practice is to regard such electrocardiographic changes as being indicative of reversible myocardial ischemia unless there are clinical signs of myocardial infarction. Furthermore, many authorities on electrocardiography warn against exaggeration of slight abnormalities. This attitude is natural, since the reversible changes in the S-T segment and T wave are frequently observed after exercise tests and with emotional strain.

However, this optimism is not always justified. Mathewson and Varnam reported a small number of cases in which the electrocardiograms showed only primary T-wave changes, but which later developed into cases of clinically recognizable coronary arterial disease. In some of these cases myocardial infarction was demonstrated at autopsy.

The first step that we considered in this

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Fig. 11 (1 Case examples of bend scardial afarc tion produced by inject n of b tances of high m lecular wei ht nd other b-t es) 1 C t urface of the heart of a rabbit which recei ed gl cogen (15 m hg) serotonin (10 μg kg) nd epinephrine (10 μg kg) intra enon l three times week for 4 week Gra b whi foci of nf tion can be seen in the bc locardial layer of the left entricle almost circular except for the lateral wall The lesion has been outlined b black d tted line

in estigation was the collection of tatisti cal data on the incidence of findings of sub endocardial infarcts and infarct like lesions in postmortem examinations of patients with certain electro ardiographic changes such as depression of the S-T segment and inversion of the T wave However it is difficult to collect the necessary data be cause patients do not u ually come to autopsy simply because of conditions which cause segmental depression or T wave in version alone

Recently the authors (Shimamoto and associates[4]) succeeded in producing myo-cardial infarcts and infarct like lesions after inducing coronary arteriosclerosis in rab-bits guinea pigs and rats the ascular lesions resembled those of human arterio-sclerosis The myocardial lesions were pro-duced by administering various substances of high molecular wei ht epinephrine and other drugs described later This experi mental method is superior to various con entional methods of producing infarction such as ligation of the coronary arteries or cauterization of the cardiac wall because we could produce the lesion without open ing the chest Although the animal experi ment has its own shortcomings in compari son with findings in the autopsy of human beings the former is more definitive The animal can be sacrificed and examined at any time when it hows electrocardio-graphic evidence of segmental displacement or T wave change alone Therefore the myocardium can be studied not only when the electrocardiogram hows the typical changes of infarction but also when there are only transient changes in the S-T seg ment or T wave The myocardium can be studied thoroughly by serial sections Rab bits which were first used in producing myocardial infarction by the above men tioned method are suitable for studying this problem



Fig. 1B C t urface of the heart of a rabbit which received l teteral pol saccharide (50 μg/kg) epinephrine (10 μg/kg) nd angi ten in (3 μg/kg) int enon l) three times week for 4 week Foci f infarction milar to those hown in Fig. 1 1 ca be se in the ubendocardial la er f the poster wall of the left entricle The lesions are utlined b the black nd white d tted lines

Employing the same method we also investigated subendocardial infarction since pure subendocardial infarction was frequently produced by the above mentioned method Spatial vectorcardiograms were recorded also in the hope that they might afford a diagnostic method when the electrocardiograms failed to show apparent QRS changes

Material and methods

One hundred and eighty four young male rabbits which ranged in weight from 2 0 to 2 8 kilograms were employed for this study Fifteen rabbits were used as controls The other rabbits were studied primarily for testing whether arteriosclerosis and myocardial infarction are induced by some of certain substances and prevented by others The substances employed for testing the efficacy of inducing these changes were substances of high molecular weight such as bacterial polysaccharide nonpathogenic Escherichia coli (U5/41) glycogen dextran and kaolin various amines such as epinephrine and serotonin octapeptides such as angiotensin and fatty substances such as cholesterol and lanolin These substances were shown by Shimamoto and associates to produce swelling of the vascular endothelium and white thrombi as the immediate reactions This finding was supported by direct observations using Sandison Clark s technique as well as by indirect observations of a decrease in platelet count in the peripheral blood Later arteriosclerotic lesions and myocardial infarcts and/or infarct like lesions were produced These substances may be called *arteriosclerogenic* (Shimamoto) Various antibiotics such as penicillin streptomycin and chloramphenicol were also employed to obtain effects similar to those of bacterial polysaccharide They were selected according to their bactericidal effects in the colon when administered orally The substances employed for testing the efficacy of preventing arteriosclerosis and myocardial infarction were magnesium chloride chlorothiazide and reserpine All of these were administered in doses which proved to be effective in preliminary experiments Details on the effects of these substances and their significance have been reported elsewhere The present report on subendocardial infarcts and infarct like lesions deals with a correlation



Fig 1C Microscopic findings in the ventricular septum of the same rabbit heart shown in Fig 1B Small discrete scars and granulation tissue with calcification can be noticed (Hematoxylin eosin stain Magnification ×)

between the pathologic findings and the electrocardiographic and spatial vectorcardiographic findings.

Electrocardiograms were taken in all 184 rabbits. Their control records were normal. The test substances were given for 4 or 8 weeks, and electrocardiograms were taken every week before and during administration. When electrocardiograms showed significant changes or after administration of the test substances for 4 or 8 weeks, the animals were sacrificed for autopsy after electrocardiograms were taken. The standard limb leads, unipolar limb leads, and the standard precordial leads were always taken, and in addition Leads V, V, V and V were taken occasionally. Because of the structural difference between the rabbit and the human body, Leads V_1 and V were obtained at the level of the fifth intercostal space and Lead V, V_4 and V_6 were obtained at the level of the sixth intercostal space.

Spatial vectorcardiograms were recorded on 25 rabbits. In each rabbit they were taken by two methods, by that of Duchosal as modified by Grishman (designated as Grishman's method in this paper) and by that originated by Wilson and developed by Burch (designated as Burch's method). By the former technique, four electrodes were placed to construct the cube with the first electrode at the level of the fifth dorsal vertebra, which was a slightly different arrangement from that described by Grishman because of the structural difference from the human body. In the use of the second method a slight departure was made from Burch's original plan. The horizontal plane and not the tilted superior plane of the equilateral tetrahedron was thought to be obtained by combining Lead I and Lead V_8 using Wilson's central terminal multiplied by the same coefficient as reported by Burch and associates.[9]

Almost all of the animals were sacrificed by air embolism after the test substances had been administered for 4 or 8 weeks. Some of them were sacrificed when the occurrence of significant electrocardiographic and/or vectorcardiographic changes were observed. Immediately after autopsy, all internal organs were fixed in neutral formalin and Carnoy's fixative for subsequent histochemical study. Each organ was weighed and observed macroscopically, and the usual pathologic examination carried out using hematoxylin and eosin, elastica van Gieson, toluidine blue, and Altmann-Kull's mitochondrial stains. Altmann-Kull's technique was found to be a very suitable method for determining the small coagulative degeneration of the myofiber of the myocardium. To demonstrate calcium, von Kossa's silver nitrate technique was applied on the slide slightly counterstained with hematoxylin and eosin. In order to demonstrate the deposition of fat, Sudan III was also used.

Results

There were no pathologic findings in the hearts of the 15 control rabbits nor in 1 of 6 rabbits to which serotonin alone was administered. Their electrocardiograms showed no abnormal findings.

Autopsy showed myocardial infarction or infarct-like lesions grossly or histologically in all of the other 168 rabbit hearts. Large solid transmural infarcts were noticed in 6 of these hearts. The electrocardiograms of these 6 animals showed typical infarction patterns with appearance of an abnormal Q wave, elevation of the S-T segment, and symmetrical T wave inversion. They were excluded from the main subject of our study since the findings were classic. In the other 162 hearts, most of the lesions were found in the subendocardial region, in the papillary muscle of the left ventricle, and in the ventricular septum (Fig. 1). The outermost one third of the ventricular wall was not involved. Some of the lesions were large solid infarcts, others were small isolated irregular scars a few millimeters in diameter which tended to coalesce. In others, coagulation necrosis or vacuolization of several myocardial fibers was noted by microscopic examination. Since larger solid subendocardial scars and multiple small scars with intervening areas of nonscarred tissue are expected to yield different electrocardiographic findings, the pathologic alterations were classified into four groups (see Table I) and were compared with the electrocardiographic findings in these rabbits.

As for the S-T-T changes shown in Table I, a positive sign indicates depression of the S-T segment and/or flattening or

inversion of the T wave. Although in many such cases S-T depression and T wave inversion were quite evident and could not be regarded as the results of changes in rate, it seems unnecessary to show such illustrative cases here because these changes were classic. Remarkably, no changes were noticed in the S-T segment and T wave in 9 of 46 cases of solid subendocardial infarcts and in 15 of 50 cases of spotty fibrosis alone. Equivocal changes were observed in 17 cases of solid subendocardial infarcts and in 16 cases of spotty fibrosis alone. The changes were depression of the S-T segment

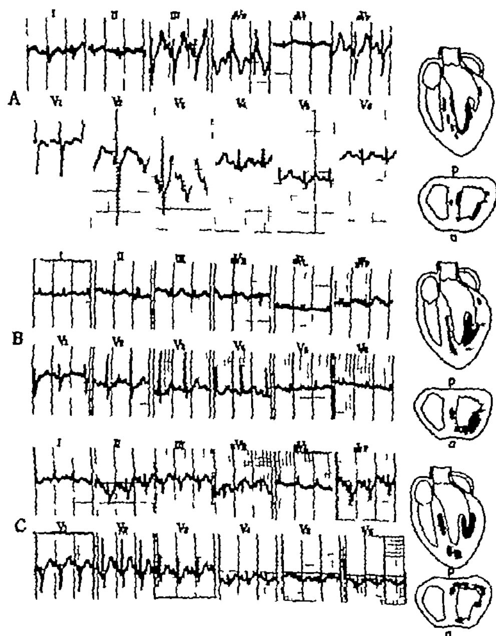


Fig. 2. Examples showing either no changes or minor S-T, T changes [illegible] the electrocardiograms [illegible] definite subendocardial infarction was present. In all three cases larger solid subendocardial infarcts together with multiple spotty fibrosis and small intramural scars were found at autopsy. All electrocardiograms were taken *just before* the animals were sacrificed. In the cross-sectional diagrams of the heart, a and p denote anterior and posterior surfaces of the heart, respectively.

Table I Correlation of electrocardiographic and pathologic findings in subendocardial infarction and infarct like lesions with normal controls

ECG findings	*Pathologic alterations*			
			Macroscopic lesion	
	No pathologic changes	*Microscopic lesions*	*Spotty fibrosis and small intramural scars*	*Large solid subendocardial infarcts and scars*
QRS changes				
−	16	60	47	44
±	0	4	3	4
+	0	0	0	0
S-T T changes				
−	16	21	15	9
±	0	20	18	17
+	0	3	17	22

− No change ± Change noted only when compared with the control electrocardiogram [illegible] decrease [illegible] amplitude of R F[illegible] QRS changes
+ Abnormal Q wave F[illegible] S-T T changes + S-T depression [illegible] 0 1 mv and/or T wave [illegible]

of less than 0 1 mv or slight flattening of the T wave noted only after comparison with the control electrocardiograms It was our impression in many cases that no pathologic alterations would be found because of a lack of any significant changes in the electrocardiograms but at autopsy some fibrosis or infarction was almost always discovered Fig 2 shows three such cases of either no electrocardiographic changes or equivocal S T T changes but with definite autopsy findings of some fibrosis or infarction

Table II Diagnostic value of the vectorcardiogram and the electrocardiogram in subendocardial infarct and/or infarct like lesions in cases in which both were taken

Diagnostic value	*Number of cases*
Both in vectorcardiogram and in electrocardiograms	8
In vectorcardiograms but not in electrocardiograms	5
In electrocardiogram but not in vectorcardiogram	0
Neither in vectorcardiograms nor in electrocardiograms	10
Total	23

In Table I significant decrease in the amplitude of R is noted Although some of the cases included in this table showed definite changes in the QRS wave in comparison with the control records none of the cases showed a definitely abnormal Q wave

Although abnormal Q waves rarely appeared in these cases a decrease in amplitude of the R waves was frequently noticed when comparison was made with control electrocardiograms This relation was more evident in anteroseptal infarction probably because the area of infarction was close to the exploring electrode of Leads V_1 and V_2 This is seen in the electrocardiograms of Fig 6 where R is lower in *C* than in *A* However it was occasionally difficult to explain this in a single case For example in Fig 3 the autopsy evidence of anterior infarction may make one regard the decrease in R_{V1} in *B* as compared with R_{V1} in *A* as evidence of infarction but R_V in *B* is higher than R in *A* Nevertheless a study of all of the 20 cases which showed infarcts or scars in the subendocardial layer of the anteroseptal region reveals some tendency of diminution in the amplitude of the R waves (Fig 4) In this figure the amplitude of the R wave of Leads V_1 and V_2 of the control electrocardiograms is taken as

the abscissa and that recorded immediately before the animals were sacrificed is taken as the ordinate It can be pointed out that some cases in which there were gross solid lesions or multiple gross spotty fibrosis showed a marked decrease in the amplitude of the R wave whereas almost none of the cases in which there were microscopic lesions alone showed a comparable decrease However if we take a smaller change in amplitude no special tendency can be noted There are many factors to alter the amplitude of the R wave Change of position of electrodes rotation of the heart pulmonary embolization and ventricular hypertrophy all can cause such alteration Since these factors obscure evidences of infarction we were interested in cases which showed marked decrease in the R wave In these cases we did not find either pulmonary emboli or detectable ventricular hypertrophy Although slight change of the electrode position and rotation of the heart could not be excluded completely we believe that anterior infarction was usually the cause of the decrease in the R wave Considering all of the 20 experiments we can state at least that anterior infarction is one of the causes of the decrease in the R wave in the right precordial leads

Although vectorcardiograms were taken primarily by the two methods in 25 rabbits as stated above only those obtained by Grishman s method were successively recorded because in rabbit they showed a more consistent configuration in the control record as seen in Fig 5 Twenty three of 25 animals were included in the study of subendocardial infarction and infarct like lesions The value of the vectorcardiogram

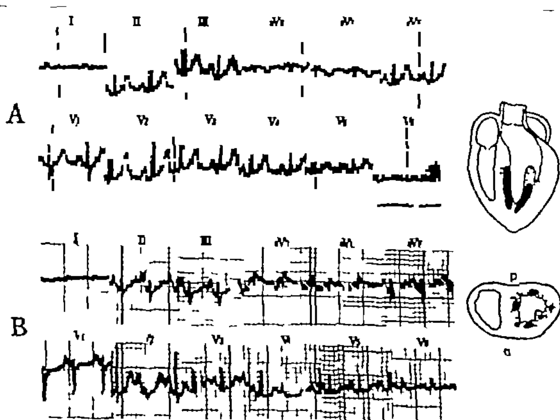


Fig 3 An example of marked decrease in the amplitude of the R wa in Lead V in the presence of antero-septal subendocardial infarction A is control record B is the record taken just before sacrificing the anim l to which substa of high mo lar w gh had been adminis t red for 30 da At autopsy sol d infarcts together ith mult ple spotty f brosis and small intramural scar ere noticed almost ircular in the subendocardial layer of the left entricle especiall marked in the anteroseptal region and p denote terior nd posterior surfaces of the heart respectively As for the increase in amplitude of the R e in Lead V in B see text

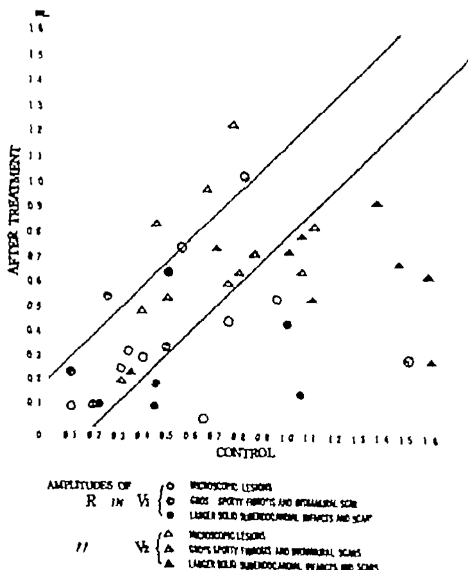


Fig. 4. Changes in amplitude of the R wave in the right precordial lead in the presence of anterior subendocardial infarct or infarct-like lesions. The space between the two oblique lines is the insignificant area because of the minute changes in the amplitude.

was more limited than we expected because the QRSsÊ loops showed little change, as might be expected from the slight change in the QRS waves of the electrocardiograms, and also because the S-T-TsÊ loops were in many cases too small to give a more accurate diagnosis than that given by the electrocardiograms.

Nevertheless, vectorcardiograms showed diagnostic features of infarction in 5 instances in spite of the fact that the electrocardiograms showed no significant abnormality (see Table II). The vectorcardiographic diagnosis was related in 4 of 5 such instances to anteroseptal infarction, in which case there was a diminution of the initial anterior portion of the QRSsÊ loop in the horizontal plane. In these 4 cases this diminution was apparent without comparison with the control vectorcardiograms, whereas either no significant decrease in amplitude of the R wave was observed or such decrease was first noted only after comparison with the control electrocardiogram. An illustrative case is shown in Fig. 6.

Discussion

It is remarkable that irreversible structural myocardial lesions were found so frequently at autopsy regardless of the pre-

ence or absence of minute depression of the S T segment and without T wave inversion in the electrocardiograms This finding was so marked that Table I might give the im pression that whether the S T T changes exist or not makes no difference in the inci dence of myocardial lesions However when slight S T T changes which could be re

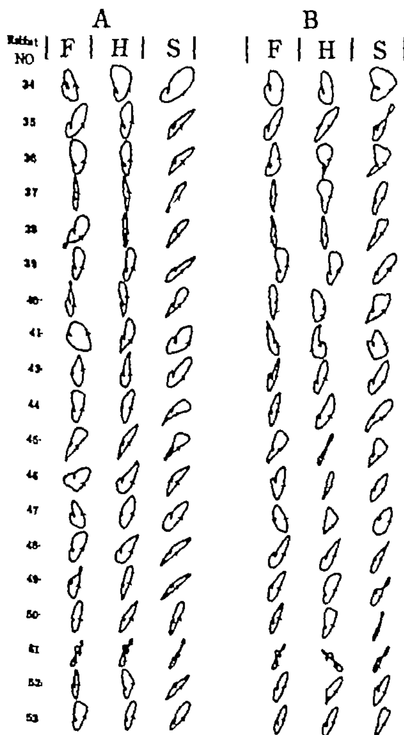


Fig 5 Vectorcardiograms obtained the control period of normal Rabbit A By Grishman method B By Burch method F, H S Frontal horiz tal sagittal planes respectively

garded as significant only after comparison with control records were included as positive S-T-T changes, more than two thirds of the cases with myocardial lesions showed positive S-T-T changes. Therefore, it is not the nonexistence of the S-T-T changes but their slightness that should be noted. Another point to be emphasized in regard to Table I is that there is little difference in the incidence of positive S-T-T changes among the three groups, i.e., microscopic lesions and smaller and larger macroscopic lesions. This is probably because the S-T-T changes are not findings corresponding to myocardial destruction, to which chief attention was paid in this pathologic examination, but to the subnecrotic changes. Myocardial destruction can be inferred only indirectly, at best, by the S-T-T change.

Care should be taken in applying our findings directly to human coronary insufficiency, but they should be borne in mind when electrocardiographic interpretation is made. Our results suggest that slight segmental depression or T-wave changes should not always be regarded merely as indicating a reversible myocardial injury or ischemia, even if no other clinical signs of infarction exist.

Burch and associates pointed out that in autopsies of human beings multiple coalescing small scars were found mostly in patients who died from causes other than heart disease. In the autopsy of human beings with infarction, it is rather rare, however acute the infarction may be, that one sees only pure acute changes as found in experimental acute infarction. Usually, chronic changes are mingled with acute ones. We cannot expect patients with coronary sclerosis to come to autopsy merely because of small myocardial scars, but it is quite possible that repetition of similar causes will eventually lead to solid myocardial infarction. Therefore, it is important to recognize these changes.

As for the changes in the QRS complex in the case of subendocardial infarction, there have been many controversies. Previously, Wilson and co-workers observed in experiments on the dog QR or notched QS waves in direct epicardial leads over pure subendocardial infarcts or over the subendocardial infarcts of cone-shaped transmural infarcts. But subsequent experimental studies by Kisch, Nahum and Hoff[1] and by Boyd and Scherf failed to show abnormal QRS complexes in standard limb leads, whereas the studies of Pruitt, Barnes, and Essex,[11] Hellerstein and Katz,[12] and Pruitt and Valencia[13] showed occasionally more or less of a decrease in the amplitude of the R and S waves or the appearance of small Q waves sometimes in direct epicardial leads or in Lead IV R. The reports of clinical pathologic studies are also conflicting. Pardee and Goldenberg[14] and Myers and co-workers[1, 17] found initial Q waves in precordial leads occasionally, but Levine and Ford consistently failed to obtain Q waves in precordial leads. A review of other reports showed that pathologic Q waves were recorded in some instances but not in others, both experimentally and clinically. In this respect, recent experiments by Prinzmetal and co-workers have attracted attention. According to them, precordial and epicardial leads which were recorded directly over the pure subendocardial infarct consistently exhibited normal R or RS waves or absence of abnormal Q wave. On the basis of their finding in intramural lead electrocardiograms, they concluded that the inner layers of the normal ventricular wall appeared to be electrocardiographically silent, i.e., subendocardial muscle did not affect the depolarization complex in epicardial or precordial lead. However, more recent extensive clinical pathologic reports by Cook, Edwards, and Pruitt[18, 19] again noted occasionally the loss in amplitude of the R waves, and in a few cases the presence of small Q waves in certain precordial leads. These findings were not in agreement with the theory of electrocardiographically silent subendocardial muscle.

In this study it was again proved that abnormal Q waves seldom appear in subendocardial infarction, and in this respect the findings differ from the previous reports of Wilson and others,[17] but support those of Prinzmetal[1] and others.[8] While conforming to the findings in many reports, our results show, in addition, marked decrease in amplitude of the R wave occasionally in solid subendocardial infarction and in multiple gross spotty fibrosis. This finding was noticed in the report of Prinzmetal and co-workers in their acute experiments. We

agree with Cook and associates[5,13] that subendocardial depolarization is not electrocardiographically silent. The appearance of abnormal Q waves and the decrease in amplitude of the R waves should be regarded as similar phenomena due to the effects of a different degree of myocardial destruction.

Local myocardial destruction produces tardiness and alteration in the order of local excitation. Also, since some cells are non functional, the voltage previously contributed by these will be lost. Both of these conditions increase the likelihood of local cancellation and counterbalancing by vector forces produced by normal myocardium elsewhere. In the case of subendocardial lesions the overlying myocardium still contributes endoepicardial vectors, whereas in transmural and subepicardial lesions the presence of Q waves suggests either deletion of all endoepicardial forces

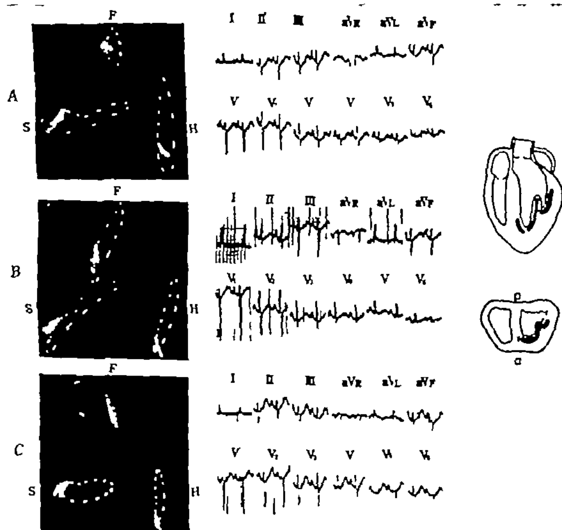


Fig. 6 An example in which the ectorcardiogram showed probable di gn t feature of tenor infarction but the electrocardiogram showed no evidence according to the current criteria. A Control record. B Record obtained after administration of sub tance of high molecular weight for 35 days. C Record taken just before the animal was sacrificed after administration of the substance for 46 da . B and C show diminution of the initial portion of the QRS sE loop in the horizontal plane which suggests anterior infarction. Autopsy revealed solid subendocardial infarct together th multiple spotty fibrosis in the anterior wall of the left entricle. and p denote anterior and posterior surfaces of the heart. In retrospect and after comparing these three electrocardiograms believ th t he diminution in he amplitude of R of Lead V in C is probably rel to anterior infarction

or total cancellation by other forces The role of the effect of proximity to subepicardial or subendocardial lesions has not yet been established

Summary

1 Various substances of high molecular weight epinephrine and other drugs were administered to 169 rabbits with formation of myocardial infarction or infarct like lesions in 168 Correlative study with electrocardiograms and autopsy findings was made together with the records of 15 other control rabbits Among these 162 rabbits with subendocardial infarcts or infarct like lesions were the subjects of this study

2 In subendocardial infarcts or infarct like lesions the incidence of depression of the S T segment or flattening or inversion of the T wave was much less than expected No S T T changes could be noticed in about one third of all of the cases in spite of the presence of the lesions at autopsy In another third the changes were so slight that they became evident only after comparison with control records These results suggest that in clinical practice slight segmental depression or T wave changes should not always be regarded as indicating a reversible myocardial injury or ischemia even if no other clinical signs of infarction exist

3 As for QRS changes due to subendocardial infarcts or infarct like lesions a definitely abnormal Q wave appeared in none of the cases However especially in the examination of 20 rabbits which showed infarcts or infarct like lesions in the subendocardial layer of the anteroseptal region a marked decrease in the R wave in the right precordial leads was encountered occasionally when the lesions were relatively large

4 Vectorcardiograms in addition to electrocardiograms were obtained in 25 rabbits The vectorcardiograms showed diagnostic evidence of infarction in 5 instances in which the electrocardiograms showed no significant abnormality In most of them the abnormal change was diminution in the initial anterior portion of the QRSsÊ loop due to subendocardial infarcts or infarct like lesions in the anteroseptal region

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Peripheral and central arterial pressure pulse in the estimation of the severity of aortic stenosis

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Since aortic stenosis has been accessible to surgical treatment, numerous attempts have been made to estimate the degree of the aortic stenosis by studying either the indirect or direct peripheral and central arterial pressure pulses.[1] The carotid arterial curves were the most extensively studied among all indirect pulse tracings.[4]

With the introduction of left heart catheterization, accurate measurements of the pressure gradient across the stenotic valve could be obtained. When combined with right heart catheterization, the pressure-flow relationship could be calculated and thus the size of the aortic valvular orifice could be fairly well estimated.

The left ventricular pressure may be recorded by catheterization of the left heart, either by a puncture through the posterior chest wall,[12] a bronchial wall,[14] or the anterior chest wall.[4] In the majority of these studies the pressure gradient between the left ventricle and the brachial artery was measured.

The purpose of this paper is to report the observations on the pressure gradient and the pressure-flow relationship in 26 patients with aortic stenosis, either pure or in combination with other valvular diseases. The left ventricular pressure was recorded by retrograde catheterization via the brachial artery.

The pressure gradient and the pressure-flow relationship between the left ventricle and the aorta as well as between the left ventricle and the brachial artery were studied. It is noted that there was in some cases a negative pressure gradient between the left ventricle and the brachial artery, i.e., a higher systolic pressure in the brachial artery than in the left ventricle, whereas a positive pressure gradient between the left ventricle and the aorta was always found.

However, when the area of the aortic valve was calculated from the pressure pulses either of the aorta or the brachial artery, there was a fairly small difference between both values, even in those cases in which the systolic peak pressure was much higher in the brachial artery than in the aorta.

Material and methods

Combined catheterization of the right and left heart was performed in 26 patients with aortic stenosis of different degrees of severity, either pure or in combination with other valvular diseases. In all patients a clinical diagnosis was established and

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aortic valvulotomy has been under consideration. There were 8 women and 18 men; they ranged in age between 5 and 48 years.

Right heart catheterization was first carried out in the usual manner via an antecubital vein. After the pressures had been recorded in the right heart, including the pulmonary arterial wedge pressure, the tip of the catheter was positioned in the pulmonary artery and a Cournand needle was inserted into the brachial artery. Expired air was then collected in a Douglas bag for 3 minutes. In the middle of this period samples of blood were withdrawn from the pulmonary artery and the brachial artery.

Catheterization of the left ventricle was then performed in a retrograde way via the brachial artery; the technique is detailed elsewhere.

The cardiac output was calculated by the direct Fick method. Blood oxygen was determined by the manometric method of Van Slyke.[11] The respiratory gas analysis was carried out by means of the Scholander method.[12] The zero level for the recorded pressures was taken at 5 cm below the angle of Louis of the patients in the supine position. The mean pressures during systolic ejection of the left ventricle, the aorta, and the brachial artery were obtained by planimetric integration of the systolic portions of the phasic records.

The areas of the aortic valves were calculated according to the formula of Gorlin and Gorlin (*see at bottom of page*).

The systolic ejection period was obtained by superimposing the aortic tracing and the brachial arterial tracing on the left ventricular tracing by means of the simultaneously recorded electrocardiogram with due allowance for pulse transmission time.

Results

The relevant data on all patients investigated are summarized in Table I.

The systolic pressure in the brachial artery was higher than that in the aorta in all but 2 patients. The diastolic pressures in the aorta were found in 3 patients to be equal to, in 19 to be higher than, and in 2 patients to be lower than that in the brachial artery.

The constantly observed pathophysiologic phenomenon in aortic stenosis was the presence of a systolic pressure gradient between the left ventricle and the aorta. In 6 patients a negative systolic pressure gradient existed between the left ventricle and the brachial artery, i.e., the systolic pressure in the latter was higher than that in the former (Fig. 1). The negative gradient ranged from 2 to 39 mm. Hg. However, the mean systolic pressure was always higher in the left ventricle than in the aorta and brachial artery as well. This mean systolic pressure gradient ranged from 6 to 60 mm. Hg for the aorta and from 6 to 55 mm. Hg for the brachial artery.

A comparison of the gradient, flow, and calculated valvular areas employing the brachial arterial and aortic tracings is made in Table II. In general, there was a good agreement between the two methods of calculation.

Discussion

In aortic stenosis there is obstruction to the flow of blood from the left ventricle

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$$A.V.A.\ (cm^2) = \frac{A.V.F.}{44.5 \times \sqrt{L.V._m - AO(BA)_m}}$$

$$A.V.F.\ (ml/S.E.P.\ second) = \frac{C.O.}{S.E.P. \times H.R.}$$

A.V.A. (cm^2)	= aortic valvular area
A.V.F. (ml/S.E.P. second)	= aortic valvular flow
$L.V._m$ (mm. Hg)	= mean systolic ejection pressure of left ventricle
$AO(BA)_m$ (mm. Hg)	= mean systolic ejection pressure of aorta (brachial artery)
C.O. (liters/minute)	cardiac output
S.E.P. (sec.)	= systolic ejection period per beat
H.R.	heart rate

Tabl I Hemodynamic studies in 26 patients with aortic stenosis either pure or in combination

Number	Patient	Age (y)	Sex	Cardiac output (L/m)	Cardiac index (L/min/sq cm B S)	Pulse rate	Pressure (mm Hg) LV Systolic/diastolic	LV Systolic mean	Aorta Systolic/diastolic	Aorta Systolic mean
103	Fa	17	M	4 6	3 1	143	170/0	110	94/59	70
109	Gr	32	F	4 3	2 3	70	180/0	170	135/64	95
69	?	23	M	4 4	2 0	76	116/3	100	104/71	89
713	d Wa	17	M	8 0	4 5	107	124/0	104	96/58	76
704	Go	12	M	6 8	5 0	130	133/0	118	100/73	88
475	Ra	5	M	3 9	5 0	127	137/	115	100/73	88
726	d Po	16	M	8 9	6 8	94	127/5	103	109/78	93
741	R j Ra	24	F	5 4	3 0	80	15?/3	123	96/59	72
762	Ho	44	M	5 5	3 4	91	160/0	94	9 /54	67
739	Tey	11	M	7 0	5 5	111	149/0	107	100/73	83
823	De Ou	43	F	4 7	4 0	81	127/5	96	97/64	68
847	R	15	F	4 7	3 1	83	160/0	124	80/50	64
872	Ha	12	M	5 3	4 0	120	107/3	86	87/68	72
884	Goe Dij	36	F	5 4	3 2	91	98/0	90	77/45	76
916	Bo	48	M	5 5	2 9	73	114/0	98	9?/60	76
903	de Gro	29	M	6 1	3 6	73	100/0	91	93/55	79
972	La Kh	24	F	6 8	4 3	178	173/6	127	93/59	76
942	Gr Neu	46	F	4 8	3 1	109	179/0	119	112/73	78
943	Ke	16	M	7 6	3 9	115	123/5	92	77/65	70
947	Da	??	M	6 3	3 0	87	135/5	125	114/76	101
953	Ke	17	M	6 4	3 8	109	106/0	90	85/64	78
968	Keu	8	M	5 0	4 0	118	111/8	93	93/58	75
974	Moe	25	F	5 1	3 4	105	164/0	115	72/44	64
1077	Ve	21	M	5 2	2 7	87	142/5	105	117/81	99
1176	de Boe	58	M	6 4	3 2	61	150/0	117	104/56	77
1173	Ie	14	M	7 6	5 4	106	137/2	115	96/72	85

AS A rt stenosis, MS M tral st nos s.

with other valvular diseases

Brachial artery		Systolic mean gradient L1 10 (mm Hg)	Systolic ejection period (sec/min)	Aortic valvular flow (ml/min)	Size of aortic valve (sq cm)		Diagnosis
Systolic/diastolic	Systolic mean				Calculated	Palpated	
119/33	8	40	39 6	117	0 4	0 5	Supravalvular AS (pure)
139/54	105	25	2) 0	153	0 7	1 0	Severe AS (operated) MS (operated)
139/66	93	11	2 0	700	1 4	—	Slight AS (pur)
116/34	80	78	20 4	39	1 6	—	Slight AS (pure)
116/64	99	30	25 0	272	1 3	—	Moderat AS mild aortic regurgitation
103/68	90	77	23 8	164	0 7	0 8	Severe pure AS (operated)
142/69	95	10	20 7	430	3 1	—	Slight AS (pur)
1 2/5	76	51	23 9	226	0 7	1 0	Severe AS nd MS (both operated)
104/51	82	37	28 8	191	0 7	—	Severe AS nd aortic regurgitation
112/73	93	24	24 5	286	0 9	1 0	Severe pure AS (operated)
97/61	68	28	20 2	332	1 4	0 8	Severe pure AS (operated)
80/45	69	60	23 5	700	0 6	1 0	Severe pure subval ular AS (operated)
97/62	79	14	26 4	701	1 3	—	Moderat pure AS
86/45	84	14	25 0	215	1 3	—	AS a d aortic regurgitation mitral regurgitation nd light MS
100/58	88	22	24 0	779	1 1	—	Severe MS (operated) severe AS light aortic regurgit tion
98/48	81	12	23 4	761	1 7	—	Slight AS light mitral regurgit tion slight to moderate MS
110/60	81	51	35 0	195	0 75	0 8	Severe pure subvalv lar AS (operated)
138/65	88	41	30 0	160	0 75	1 0	Severe AS nd MS (both operated)
93/67	75	2	32 0	37	1 1	1 0	Severe pure AS (oper ted)
144/70	100	24	24 4	58	1 2	—	Slight AS (pure)
108/61	80	1	34 0	188	1 2	—	Moderate MS (operated) slight AS nd aortic regurgitation
114/57	82	18	32 0	156	0 9	—	Moderate pure subvalvular AS (operated)
135/47	75	51	25 0	204	0 75	1 0	Se ere AS nd MS (operated)
15 / 2	99	6	23 0	276	2 0	—	Mild bval ular AS (pure)
126/36	9	40	23 1	268	0 95	—	AS (pure)
114/71	94 5	30	27 6	276	1 1	—	AS (pure)

Table II Comparison of systolic mean pressure systolic mean pressure gradient flows and areas in aorta and brachial artery

No	Patient	Systolic mean pressure LV	AO	BA	Systolic mean gradient LV AO	LV BA		SET AO	BA	AO	BA	%	AVA AO	BA	%
1	I	110	70	78	10	32	20	31 3	37 2	131	121	7	0 5	0 5	0
2	(	120	95	105	25	15	40	23 1	25 9	186	166	11	0 8	1 0	25
3	R	115	88	90	27	25	7	30 1	33 0	129	118	7	0 5	0 5	0
4	/	100	83	73	11	7	56	19 8	21 1	222	203	8	1 5	1 7	13
5	(	118	88	79	30	19	37	27 3	28 6	253	238	1	1 0	1 2	20
6	d W	104	76	80	28	24	14	25 7	27 8	311	288	11	1 1	1 3	0
7	d I	103	73	75	10	8	20	20 7	22 6	140	131	8	1 0	3 1	1
8	I s	107	83	93	13	11	12	29 7	23 7	236	236	0	1 1	1 4	27
9	R j R	123	72	76	51	47	8	25 6	26 1	211	203	3	0 6	0 6	0
10	H	73	67	82	27	22	18	30 0	30 0	183	183	0	0 7	0 9	28
11	D O	96	68	68	28	28	0	23 5	21 3	285	276	3	1 2	1 4	17
12	K	123	61	63	60	55	8	21 1	28 2	195	167	11	0 5	0 5	0
13	H	86	72	73	14	7	50	21 0	27 6	221	192	13	1 3	1 6	23
14	(Dy	90	76	81	14	6	57	19 2	19 2	281	281	0	1 7	2 6	53
15	d (	93	73	81	12	10	17	18 4	19 0	336	321	4	2 2	2 3	5
16	I	98	76	88	22	10	53	18 5	13 7	301	279	7	1 1	2 0	13
17	J Kh	127	76	81	51	36	10	30 7	30 7	222	222	0	0 7	0 7	0
18	(N	113	78	85	33	31	21	27 2	28 3	176	163	1	0 6	0 7	17
19	Ko	92	70	75	22	17	23	31 0	32 2	245	238	3	1 2	1 3	8
20	D	125	101	101	24	24	0	21 8	21 5	283	268	7	1 3	1 2	8
21	Ka	90	78	80	12	10	17	21 0	25 1	267	253	4	1 7	1 8	6
22	Ka	93	75	8	18	11	30	30 7	30 7	165	165	0	0 9	1 1	22
23	M	115	64	75	51	10	21	25 2	25 2	202	202	0	0 6	0 7	17
24	N	103	79	97	6	6	0	16 5	17 1	115	233	5	2 9	2 7	7
25	I t	115	85	91	30	21	33	27 6	28 6	275	266	3	1 1	1 1	18
26	K B	117	77	92	40	25	37	20 2	20 2	317	317	0	1 1	1 1	27

D ... 55 85 ... 13 V SI ... 3
... I ad ... I d ... 113 ... fan ... I
D ... d I ... ad ... I ... m

In an attempt to maintain the aortic valvular flow there is increase in the ventricular systolic pressure with the establishment of a pressure gradient across the aortic valve during the systole. This pressure gradient is a constant pathophysiologic phenomenon in this disease provided that the narrowing of the aortic orifice is severe enough.

Most investigators have used the brachial arterial pressure in the measurement of the systolic gradient across the aortic valve and in the estimation of the size of the aortic orifice.

It has been shown by Wright, Toscano, Barbosa and Brandenburg[2] that the form of the central pressure pulse is transmitted to the periphery more faithfully in persons with aortic stenosis than in normal persons. In a previous paper it was pointed out that the systolic peak pressure in the brachial artery is almost constantly higher than that in the aorta. In cases of severe aortic stenosis, however, both systolic pressures may be equal.

In the present study it is noted that in cases of moderate to severe aortic stenosis (area of the aortic valve less than 1.0 sq. cm.) the systolic pressure was always higher in the left ventricle than in the brachial artery. However, in some cases of mild aortic stenosis (area of the aortic valve more than 1.0 sq. cm.) the reverse may happen. This was already observed by Brock and co-workers.[3]

The pressure gradient across the aortic valve has too great a range to permit the use of pressure alone in the assessment of the degree of aortic stenosis,[2] for the gradient is a function not only of the

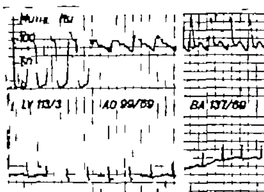


Fig 1 Pressure pulses showing a positive systolic pressure gradient between the left ventricle and the aorta but negative gradient between the left ventricle and the brachial artery

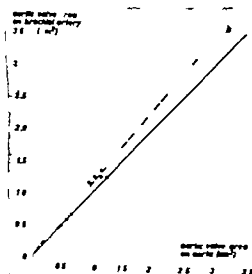


Fig 2 Comparison of area of aortic valves as calculated on tracings from aorta and brachial artery See text Line of identity b Regression line

severity of the obstruction but of the aortic blood flow as well The blood flow varies with the circumstances under which it is measured This emphasizes the importance of measuring both the pressures and flow at the same time and relating them to one another

The aortic valvular areas calculated by means of the brachial arterial pressure pulse were compared with those obtained from the aortic tracings Because of the great difference in the systolic peak pressure between the central and peripheral tracings one would expect a discrepancy between the values obtained by the two methods.

Surprisingly a reasonable agreement between both methods was found even in those cases in which a negative systolic pressure gradient between the left ventricle and the brachial artery was found (Fig 2) If a line of identity (line a) is drawn in this figure the agreement in cases with aortic valvular area of 0 75 sq cm or less is even greater This supports the finding of Goldberg and associates in their study which included only cases of severe aortic stenosis

In order to see whether there was a relation between the two calculated values of the aortic valvular area a linear regression was assumed having the equation y = a x (where y is the value on the aorta and x that on the brachial arterial tracing) The constant coefficient was omitted because when the aortic valvular area as calculated on the aortic tracing is zero that on the brachial arterial tracing will be zero as well

The regression coefficient was computed according to the method of the least square distances i e the perpendicular

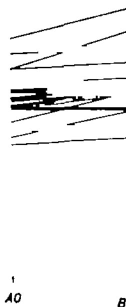


Fig 3 Comparison of systolic ejection period as measured on tracings from the aorta and brachial artery

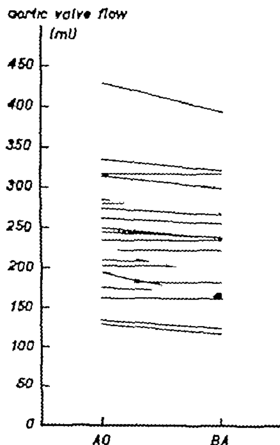


Fig. 4. Comparison of aortic valvular flow as calculated on tracings from the aorta and brachial artery.

distance from the measured point to the assumed regression line. It was found to be 1.12 with a standard deviation of 0.15; its 95 per cent confidence interval ranged from 1.07 to 1.17 (t test).

The correlation coefficient was calculated according to the normal procedure and was found to be 0.96; its 95 per cent confidence interval ranged from 0.91 to 0.96 (Fisher's z transformation).

In order to explain the reason for a similar result by both methods the following points are emphasized. (1) The systolic ejection period as measured on the brachial artery is equal to or slightly longer than that on the aorta (Fig. 3). Thus the calculated aortic valvular flow is the same in both cases or is smaller in the former case than in the latter (Fig. 4). The difference in percentages of the aortic value ranges from 0 to 13 per cent. (2) The systolic mean pressure as measured on the brachial artery, too, is equal to or higher than that measured on the aorta (Fig. 5). Consequently, the systolic mean pressure gradient between the left ventricle and the brachial artery is equal to or smaller than that between the left ventricle and the aorta (Fig. 6). The difference in percentages of the latter mounted from 0 to 57 per cent.

One can see from Table II that in most of the cases the calculations using the values for the brachial artery show not only a smaller mean systolic gradient but a smaller aortic blood flow as well. These two factors are matching with the result of similar size of aortic valvular area obtained by either of the calculation methods.

The influence of changes in the systolic mean pressure gradient and in the aortic valvular flow on the calculation by the formula of Gorlin and Gorlin is studied by

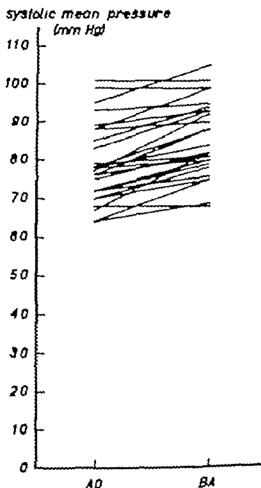


Fig. 5. Comparison of systolic mean pressure on aortic and brachial arterial tracings.

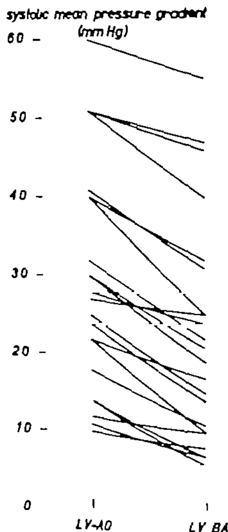


Fig. 6 Comparison of systolic mean pressure gradient between the left ventricle and aorta, and between the left ventricle and brachial artery

assuming a reduced systolic mean pressure gradient value, whereas the aortic valvular flow is kept unchanged or is diminished at the same time (by subtraction of 10 and of 20 per cent). The graph in Fig. 7 shows the percentage of error in the estimation of the aortic valvular area when the systolic pressure gradient is reduced from 0 to 60 per cent in combination with the variation of the aortic valvular flow.

As one will note, there is a change in the calculated aortic valvular area when the systolic mean pressure gradient is reduced either alone or in combination with the diminution of the aortic valvular flow. In the first case (with unchanged aortic valvular flow) the deviation of the estimated aortic valvular area will go as high as 40 per cent when the mean systolic gradient gradually decreases to 50 per cent of its original value. If there is a concomitant reduction in the aortic valvular flow, the deviation of the calculated size of the valve becomes smaller. In case of reduction in the aortic valvular flow by 20 per cent, a deviation of only 13 per cent is found at a diminution of the mean systolic pressure gradient by 50 per cent.

The average and standard deviation in Table II of (1) the decrease in the gradient when using the brachial artery as compared to the aorta, (2) the decrease in the aortic valvular flow as calculated from the brachial arterial pressure curve in comparison to the flow calculated from the aorta, and (3) the deviation of aortic valvular area as calculated from the brachial artery in relation to the value calculated from the aortic flow gradient data, have not been calculated, since it is easily noted that the values are not normally distributed.

However, in order to give a descriptive value the mean of the whole series was taken, the mean being $\frac{1}{2}(x_{12} + x_{1})$, where x_{12} and x_{1} are the values when the series were ordered according to the size of their values.

These means were found to be respectively (1) 23 per cent, (2) 1 per cent and (3) 18 per cent. Application of the values (1) and (2) to the nomogram of Fig. 7 shows an expected deviation in calculation of the aortic valvular area of about 14 per cent, which is quite close to the experimentally determined mean value (3), which was 18 per cent.

In the same frame the differences between the calculated aortic valvular areas based on the brachial arterial curves and those based on aortic tracings (in percentages of the latter values) are plotted in reference to the concomitant difference between the mean systolic gradient in the respective pressure pulses (in percentages of the values obtained from the aortic tracings) (Fig. 8). One will see immediately the fairly small difference in result between the two methods of calculation. It is in all except 5 cases within 25 per cent of the value calculated from aortic tracings, which is quite acceptable for clinical purposes. The reason for this difference is evident if the difference

in mean systolic pressure gradients is taken into account. As pointed out before, the difference will be even greater if the actual aortic valvular flow has been used.

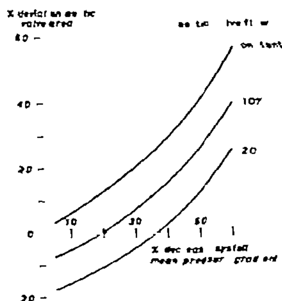


Fig. 7. Percentages of deviation of the calculated aortic valvular area when the systolic mean pressure gradient decreases either alone or in combination with a decrease in aortic valvular flow. See text.

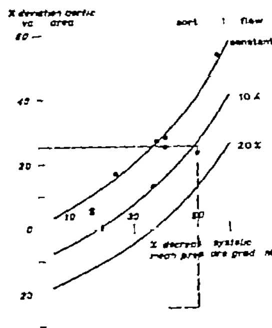


Fig. 8. Relationship between deviation of calculated aortic valvular area and decrease in systolic mean pressure gradient of the cases presented. See text.

The conclusion is that for clinical purposes the brachial arterial tracing may be used in conjunction with the left ventricular pressure in assessing the pressure gradient and the degree of severity of aortic stenosis.

Summary

Twenty-six patients with aortic stenosis either pure or in combination with other valvular diseases have been studied by combined right and left heart catheterization. The latter was carried out in a retrograde way via the brachial artery.

In moderate to severe aortic stenosis the systolic pressure in the left ventricle was constantly higher than that in the aorta or that in the brachial artery. But in mild aortic stenosis although there was a systolic pressure gradient between the left ventricle and the aorta, there could be a negative systolic pressure gradient between the left ventricle and the brachial artery.

When the calculated aortic valvular areas obtained by means of the brachial arterial and the aortic tracings were compared, the values did not differ much from each other. An explanation of this phenomenon was offered.

Thus, for clinical purposes the brachial artery may be used in calculating the size of the orifice of the aortic valve.

We wish to express our appreciation to Dr. A. Schaepkens van Riempst and Dr. A. Grundemann who performed the operations and allowed us to use their data. We further are indebted to Dr. Th. Strenger, who made the blood oxygen determinations and the respiratory gas analyses, and to Dr. L. H. van der Tweel and Dr. J. Strackee for their statistical advice.

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A method of angiocardiographic visualization of septal defects utilizing transient pulmonary artery tamponade

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Angiocardiographic demonstration of cardiac septal defects is enhanced in the presence of a right-to-left transseptal shunt.[1] However, when there is an isolated interatrial or interventricular septal defect, the transseptal shunt is, as a rule, left to right, and under these circumstances angiocardiographic visualization of the septal defect is usually impossible. An experimental method of visualizing such defects by virtue of temporary reversal of the transseptal shunt during angiocardiography has been developed.

Method

Interatrial and interventricular septal defects of 6 to 10 mm. in diameter were produced in healthy adult mongrel dogs. The technique of creation of the interatrial septal defects has been described previously. The interventricular septal defects were made by means of a similar blind punch method. Both acute and chronic preparations were obtained. The acute groups of animals underwent angiocardiographic examination immediately after creation of the septal defects. The animals of the chronic group were subjected to angiocardiography 7 to 8 months after creation of the septal defects.

Selective right heart angiocardiography performed in the routine fashion provided control studies. These control angiocardiograms were compared with angiocardiograms obtained by injection of contrast medium into the right heart complemented by balloon catheter tamponade of the main pulmonary artery. The injection catheter was introduced into the jugular vein and positioned in the right heart (right atrium for the demonstration of an interatrial septal defect, and right ventricle for the demonstration of an interventricular septal defect) under fluoroscopic control. The balloon catheter (which consisted of a No. [illegible] Cournand catheter modified to carry an inflatable balloon of 30 c.c. capacity at its tip) was threaded through the other jugular vein and positioned in the main pulmonary artery. In the acute preparation the balloon catheter, for the sake of expediency, was passed via a right ventricular stab wound into the main pulmonary artery.

After the animals had been properly positioned, the control angiocardiograms were recorded by means of the rapid film exposure technique. After a period of recovery, the test angiocardiograms were obtained by incorporation of the following

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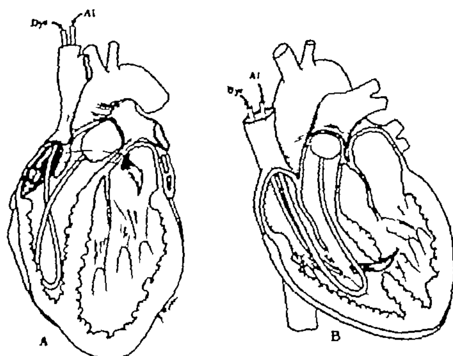


Fig 1 Artist representation of the method of demonstration of septal defect by impedance angiocardiograph (right heart angiocardiography) in conjunction with transient tamponade of the pulmonary artery) A Demonstration of an interatrial septal defect B Demonstration of interventricular septal defect

steps into the procedure (1) The pulmonary artery occluding balloon was rapidly inflated with 10 c c of room air (2) After a prearranged period of pulmonary artery occlusion varying from 0 to 15 seconds had passed the contrast medium was manually injected through the injection catheter (3) Angiocardiographic exposures were obtained again by means of the multiple film technique (4) Occlusion of the pulmonary artery was maintained during the period of x ray exposure but was immediately released upon completion of the filming process These maneuvers permitted injection of contrast medium into the right heart during a period of impeded outflow from the pulmonary artery and forced contrast medium through the septal defect (Fig 1)

Results

Only transient and reversible hemodynamic changes occurred as a result of the block in the pulmonary outflow tract The control angiocardiograms in both the acute and chronic preparations consistently failed to verify the presence of the experimentally produced septal defects Right heart angiocardiography in conjunction with balloon catheter tamponade of the main pulmonary artery failed to demonstrate transseptal passage of the contrast material in the chronic animal preparations Necropsy examination after completion of the angiocardiographic studies revealed complete cicatricial closure of the septal defects in these animals In the acute group of animals balloon tamponade of the pulmonary artery in conjunction with right heart angiocardiography verified in each instance the presence of an interatrial or interventricular septal defect by virtue of transseptal passage of the contrast bolus from the right heart into the left heart In the majority of instances the lumen of the defect itself could be visualized (Figs 2 and 3)

Discussion

Radiographic visualization of *interatrial* or interventricular septal defects by temporary obstruction of flow in the pulmonary artery by means of balloon tamponade during right heart angiocardiography

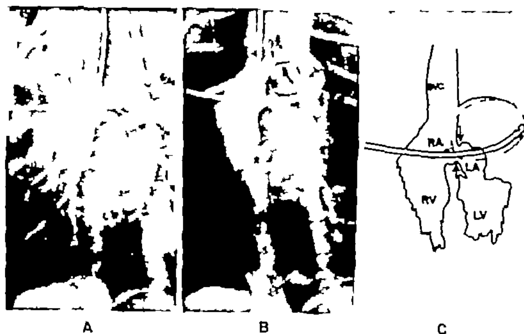


Fig. 2. Angiocardiographic demon tr tion of interatrial septal defect (left anterior oblique position 5 of Urokon 70 per cent manual injection). *A*, Control angiocardiogram showing opacification of right heart and pulmonary arteries after right atrial instillation of contrast medium through the superior ca l catheter. N contra t medium present in left heart. *B*, Angiocardiogr m in the same animal during transient balloon tamponade of the pulmonary artery howing simultaneous opacification of right heart and left heart. *C*, Line diagram emphasizing the chamber opacification present in *B*. Arrow outline early realized septal defect.

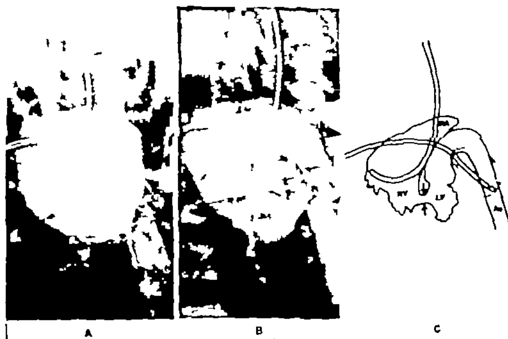


Fig. 3. Angiocardiographic demon tration of interventricular septal defect (left anterior oblique po tion 10 c.c. of Urokon 70 per cent manual injection). *A*, Control angiocardiogram fail to show opacification of the left heart. *B*, Angiocardiogram in the ame nimal during tran-ient balloon tamponade of the pulmonary artery howing imultaneous opacification of the right heart, left entricle and the aorta. Opacification of right pulmonary artery indicates incomplet block of main pulmonary artery. *C*, Line diagram empha-izing chamber opacification present in *B*. Arrows outline the defect *in muscular portion of entricula septum*.

feasible Intubation of the pulmonary artery and temporary occlusion of a main pulmonary artery by the use of balloon catheters has been performed in man without undue associated risk It seems likely that useful information as to the anatomic characteristics of interatrial or interventricular septal defects might be obtained by clinical application of this method of angiocardiography However whether or not such a method has clinical practicability is unanswered

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Investigation of arterial obstruction using a mercury in rubber strain gauge

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In peripheral vascular disease *arteriography is the only method which allows an accurate assessment of the presence of early disease the level and length of the block and is essential if direct surgery is contemplated* In the clinic however we often desire a method to indicate whether an arterial obstruction is suitable for surgical repair without using the time and expense of an arteriogram and in the long term study of patients some objective measure of their progress is required

These requirements appear to be met by the mercury in rubber strain gauge plethysmograph described by Whitney (Fig 1) which has been used to investigate the circulation to a limb in terms of segmental blood flow local arterial pressure and the volume of pulsation Investigation of the method was based on the premises that distal to an arterial obstruction there should be (a) a local reduction in arterial pressure (b) reduction in blood flow and (c) changes in the form of the recorded pulse such as a delay in its appearance a diminution of its amplitude and a slowly rising curve

Material and methods

Material Measurements have been made on 30 normal subjects on 76 with arterial obstruction and on 15 in whom arterial obstruction had been suspected but later disproved The nature of the obstruction in the 76 patients was acute embolic occlusion 2 patients atheromatous obstruction of major arteries 32 patients atheromatous obstruction of major arteries and occlusion of smaller vessels 29 patients occlusion of small vessels only 6 patients medial arteriosclerosis 7 patients

Environmental conditions The patients and subjects were studied under normal environmental conditions except when the effect of alteration of environmental conditions was being observed All measurements were made with the subjects or patients in the recumbent position

Construction and calibration of mercury in rubber strain gauge This is a rubber tube† filled with mercury when the tube is stretched the column of mercury is narrowed and its electrical resistance rises in proportion to its increase in length The gauge is connected as one arm of a Wheat

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†Latex rubber tubing (O D 0 045 in) and I D 0 014 inch) is obtainable from B F Goodrich Industrial Products Co Riverside N J



Fig 1 Strain gauge applied to calf for exercise test

stone bridge and when its resistance increases the resulting imbalance of the bridge can be recorded by a galvanometer Ebner and associates[2] describe the impedance matching circuit which we used and also the connections required for use with a Sanborn carrier preamplifier (Model 150 1100) For reasons described below we also introduced into one arm of the bridge circuit a switch by means of which a 12 500 ohm resistance could be put into circuit

The relationship between elongation of the gauge and increase in its electrical resistance is affected by the initial tension on the gauge The gauge is applied at a tension of 15 grams so that it remains in sufficiently close contact with the limb to follow its changes in dimension but is not tight enough to obstruct the venous circulation The gauge measures changes in circumference which can be used to deduce changes in volume if the cross section of the limb is regarded as being circular

In practice half a dozen gauges of different lengths are kept available and each is provided with a connection so that it can be readily plugged into circuit The gauges are calibrated in advance by a method designed to simplify calculation of the results One end of the gauge is firmly attached to a vernier scale (the moving stage of a microscope is suitable) which is fixed to an upright board A 15 gram weight is fastened to the other end by means of a thread so that the weight can hang freely Without alteration in the length of the gauge the end attached to the thread is firmly fixed to the board with adhesive plaster and the board is then laid horizontally The circuit is balanced with the gauge so fixed The length of the gauge is measured and the vernier scale is used to elongate it by exactly 1 per cent of its length The amplification is adjusted so that this change results in a deflection of 2 5 cm When this has been done the 12 500-ohm resistance is switched into circuit and the resultant deflection is recorded Thereafter whenever this gauge is used the amplification is adjusted until switching in the resistance gives the recorded deflection it then follows that an elongation of the gauge by 1 per cent will give a deflection of 2 5 cm on the record

In use a gauge first is fixed vertically with a 15-gram weight hanging from it The circuit is balanced and as the 12 500 ohm resistance is switched in and out the amplification is suitably adjusted until the deflection corresponding to the gauge is obtained The gauge is then wrapped around the limb and the circuit is brought into balance not by altering the controls but by stretching or relaxing the gauge as required when this is done it follows that the gauge is applied to the limb at a tension of 15 grams The ends of the gauge are simply fixed to the limb by means of adhesive plaster (Fig 1) No correction for temperature is made because the response of the gauge does not change sig

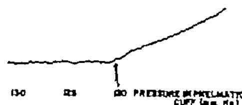


Fig 2 Measurements of systolic pressure Volume record of foot as pressure in ankle cuff is red

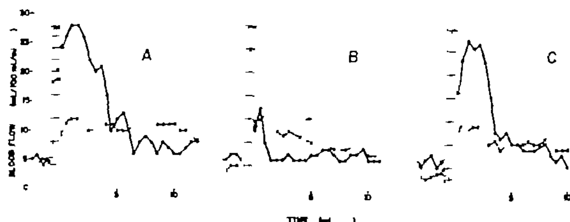


Fig 3 Blood flow through calves of patient with arterial obstruction predominantly in the left leg The blood flow through the grossly ischemic calf is shown by an interrupted line that through the more normal calf by a continuous line *A* shows the blood flow after the strenuous exercise of hopping for 1 minute and 20 seconds *B* shows the blood flow after the mild exercise of walking for 10 minutes *C* shows the reactive hyperemia after ischemia of 10 minutes duration

nificantly within the range of temperatures of the limb

Local arterial pressure In normal subjects intra-arterial pressure was measured by a capacitance manometer Blood pressure gradients along the leg were measured in the following manner The strain gauge is put around the foot and a blood pressure cuff around the ankle The cuff is inflated above systolic pressure and the pressure is then reduced in steps of 5 or 10 mm Hg until the arterial blood just begins to flow under the cuff This point is shown by a steady increase in the volume of the foot (Fig 2) Subsequently occlusion cuffs of suitable widths are placed on the calf and lower thigh so that the systolic pressure can be measured in the same way in these regions The width of the cuff used for the measurement of systolic pressure should be in accord with the girth of the limb for the thigh a cuff which is at least 18 cm in width is required

Volume pulse If the sensitivity of the recording is increased by turning up the attenuation control the strain gauge can be used to give an amplified record of the small changes in volume of the limb which occur throughout each pulse beat We have called this record the *volume pulse* Since the attenuation control increases the sensitivity by a known factor this record can be calibrated and we can use the strain gauge circuit as a quantitative and recording oscillometer (Fig 5) Oscillometer readings were also taken by means of a Collens oscillometer

Blood flow Blood flow was measured by the venous obstruction method of Hewlett and Van Zwaluwenburg Since the amplification is adjusted to give a deflection of 2 5 cm with a 1 per cent increase in length of the gauge it follows that the period of time required for inflow of blood to achieve a deflection of 2 5 cm is the time required to increase the circumference of the limb by 1 per cent If the section of the limb is circular an increase in circumference by the small amount of 1 per cent corresponds to a 2 per cent increase in cross sectional area For the purposes of translating this change into a change in volume the cross section of the limb encircled by the gauge is regarded as representing a section of limb of arbitrarily greater length and we may choose this length so that the volume of the section will be 100 ml in most limbs this would be a section of less than 1 cm in thickness When this is done the per cent changes in cross sectional area can without further calculation be written down as per cent changes in volume If from the record we find that X seconds is the time taken for a deflection of 2 5 cm to occur we can calculate that *the volume of blood flowing into each 100*

ml of limb is 2 × 60 per ... milliliter per minute

Exercise tests and reactive hyperemia The capacity of the circulation to respond to increased demands for blood flow can be determined by exercising the muscles of the limb and measuring the blood flow immediately afterward (Fig 3) The strain gauge is particularly useful for this purpose because it can be applied to the calf while the patient wears his usual walking shoes and without inconvenience to his usual gait The strain gauge can also be used for a quantitative reactive hyperemia test when the increase in blood flow which follows 10 minutes of occlusion of the circulation to the limb is measured

Results

Reliability of measurements We have confirmed the findings of Clarke and Hellon that measurements of blood flow made by strain gauge correspond with those made by volume plethysmograph The agreement at low amplification encourages the belief that the measurements of volume pulse at greater amplification may also be reliable but this cannot be readily checked The systolic blood pressure measured by strain gauge in normal subjects may be as much as 5 mm Hg below that measured by intra-arterial manometers We have not compared the two methods of measurement in patients with vascular disease however replications within 5 mm Hg are easily obtainable and we think that under optimal conditions a measured fall of 10 mm Hg is significant

Effect of varying environmental conditions Because we did not observe our patients under closely controlled environmental conditions it was important to observe what effect differences in their bodily warmth may have had on results Observations were made on 3 normal subjects in a cool state and continued as they were warmed up until a release of vasomotor tone occurred an example is given in Table I The state of warmth of the subject had no effect on the gradient of systolic pressure in the legs down to the level of the ankle When the subjects were cold and vasoconstricted

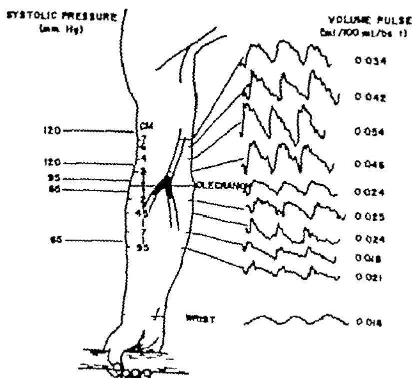


Fig 4 Systolic pressure (left) and volume pulse (right) in case of embolus to the bifurcation of the right brachial artery The figures on the arm indicate the distance in centimeters from the point of the olecranon

Table I. Systolic pressure, volume pulse, and blood flow in the lower limb of a normal subject during [illegible] warming

	Cool	Comfortable	Warm	Cool	Comfortable	Warm	Cool	Comfortable	Warm
	Thigh			Ankle			Brachial artery		
Systolic pressure	1[illegible]	1[illegible]0	1[illegible]0	1[illegible]0	120	120	1[illegible]	1[illegible]	125
Diastolic pressure (mm. Hg)	—	—	—	—	—	—	[illegible]	[illegible]	[illegible]
	Calf			Ankle			Instep		
Volume pulse (ml./100 ml. tissue)	0 0[illegible]	0 02[illegible]	0 0[illegible]	0 0[illegible]	0 01	0 0[illegible]	0 01	0 0[illegible]3	0 0[illegible]1
Blood flow (ml./100 ml./min.)	[illegible]	[illegible] 3	[illegible]	6	4 6		1 6	[illegible]	6

Table II. Circulatory measurements in the lower limbs of 2[illegible] normal subjects

	Thigh	Upper calf	Mid calf	Ankle	Instep
Blood pressure	No significant pressure gradient from arm to leg or down the leg was found				
Volume pulse (ml./100 ml. tissue)					
Mean value	0 0[illegible]	0 0[illegible]0	0 0[illegible]6	0 041	0 0[illegible]
Standard deviation	0 01	0 012	0 01	0 011	0 01
Blood flow (ml./100 ml./min.)					
Mean value	2 4	[illegible]	[illegible]6	4 1	4[illegible]
Standard deviation	1	1	1	0	[illegible]
Oscillometer readings (divisions [illegible])	[illegible]	4 [illegible]	[illegible]	[illegible]6	1[illegible]

the volume pulse in the feet was reduced but that in the more proximal part of the limbs was little affected. Since our observations were made with the patient comfortably warm we think it unlikely that the magnitude of the volume pulse could have been seriously affected by the conditions of observation. The blood flow to the feet increased as increasing warmth of the subject led to relaxation of the vasomotor tone, although as previously described no significant increase in the calf occurred. Thus environmental conditions would affect the rate of blood flow through the feet only, and we have made little use of this particular measurement.

Findings in normal subjects. The averages of measurements from [illegible]5 subjects, who were between 20 and 30 years of age, taken under the same conditions as those for the patient, are given in Table II. Allwood has shown that the blood flow in the calf does not change significantly with age, so we have used these results from younger subjects for comparison with the results obtained from patients who were 40 to 70 years old. In 4 subjects the reductions in volume pulse and blood flow in the forearm were compared as the brachial artery in the antecubital space was subjected to gradually increasing pressure. An example of the results is shown in Fig. [illegible]

Example of exercise and reactive hyperaemia tests. A, B and C of Fig. 3 show the use of exercise and reactive hyperaemia tests to measure the capacity of the circulation to respond to demands for increased blood flow. The patient was a man with a localized obstruction of the left iliac artery, which was treated by thromboendarterectomy. There was no significant circulatory obstruction in the right leg. The findings are discussed later.

Findings in different forms of arterial disease

A. ACUTE ARTERIAL OBSTRUCTION. The characteristic findings when an embolus is present are a normal circulation proximal to it and distal to it a sharp reduction in amplitude of volume pulse and arterial pressure. The distal blood flow is characteristically reduced (Fig. 4).

B. ATHEROMATOUS OBSTRUCTION OF MAJOR ARTERIES. In this condition a series of reductions of arterial pressure and volume pulse may be expected over the major arteries. Collateral circulation is so developed that it is seldom that the blood flow at rest is reduced, and a reactive hyperaemia test is required to disclose the circulatory deficiency. The results shown in Table III demonstrate how surgical relief of aortic obstruction may return to normal or near normal the reduced volume pulse and arterial pressure. In this case additional obstruction in the left popliteal artery was suggested by a systolic pressure gradient of 10 mm. Hg between the thigh and calf, and since after operation the femoral arterial pressure and this gradient were increased, the existence of a popliteal obstruction was more likely; nevertheless the improvement in circulation was sufficient to relieve symptoms.

C. ATHEROMATOUS OBSTRUCTION OF MAJOR ARTERIES AND OCCLUSION OF MEDIUM SIZED VESSELS. With extensive obstruction there is a progressive reduction in arterial pressure and volume pulse from the femoral region to the foot, but very often the blood flow at rest remains within normal limits. Eighteen of 29 patients who had wide spread arterial obstruction proved to be diabetic, 6 had been diagnosed as having thromboangiitis obliterans more than 10 years previously, and in 5 no cause for obstruction of small vessels was found. The results obtained from a patient with a combination of atheroma and thromboangiitis obliterans who had had his right leg amputated 2 years previously are shown in Table IV. From the figures obtained it was judged that the obstruction in his left leg was too widespread for arterial repair, and this opinion was confirmed by arteriogram. A sympathectomy led to sufficient increase in blood flow in the foot to permit healing of a lesion of the second toe.

D. OBSTRUCTION OF SMALL VESSELS. All patients with occlusion of small vessels only had or were suspected of having polyarteritis nodosa or disseminated lupus erythematosus. The findings are similar to those of vasoconstriction due to cold: a normal pressure down the leg, with a normal or slightly reduced volume pulse and a reduced volume pulse and blood flow in the foot. The data in Table V illus



Fig. 5. Record of volume pulses at the popliteal level from a patient with a left popliteal aneurysm.

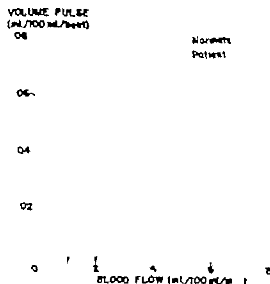


Fig. 4. Relationship between resting blood flow and volume pulse in the calf of normal subjects and in patients with obstructive arterial disease. The volume pulse affords a clear separation of normal subjects and patients; the resting blood flow does not.

Table III. Systolic pressure and volume pulse in the lower limb of a patient with atheromatous obstruction of the aorta before and after thromboendarterectomy

	Thigh		*Calf*		*Ankle*		*Brachial artery*
	Right	*Left*	*Right*	*Left*	*Right*	*Left*	
Systolic pressure (mm. Hg)							
Preoperative	55	55	55	45	50	45	125/80
Postoperative	140	130	140	110	140	110	175/80

	Thigh		*Calf*		*Instep*	
	Right	*Left*	*Right*	*Left*	*Right*	*Left*
Volume pulse (ml./100 ml./pulse)						
Preoperative	Less than 0.005 ml. per 100 ml. per pulse. Too small to be measured					
Postoperative	0.038	0.045	0.027	0.024	0.030	0.013

trate the progression of vascular disease in a 42-year-old woman in whom a diagnosis of polyarteritis nodosa was unconfirmed. She had gangrene of two toes of the left foot of 6 month duration with barely palpable dorsalis pedis and posterior tibial pulses. After she had experienced a sudden loss of sensation down the left leg, an arterial pressure gradient developed between calf and ankle, indicating an additional arterial obstruction at this time in the lower calf.

E. MEDIAL ARTERIOSCLEROSIS (MÖNCKEBERG'S DISEASE). The condition gives rise to symptoms in older men when abdominal or popliteal aneurysms develop. Such aneurysms may be blocked by thrombosis or provide the site from which emboli may pass on to obstruct distal arteries. The arterial pressure as measured by the strain gauge is usually augmented in the legs, volume pulse is sometimes but not invariably increased over a popliteal aneurysm and the blood flow is normal. The patient from whom the data shown in Table VI and Fig. 5 were obtained had expansile pulsation in the left popliteal space and persistent cyanosis and pain in three toes of the left foot. The aneurysm was demonstrated by arteriogram and subsequently relieved by excision and grafting.



Fig. 7. Volume pulse of ankle of a nondilated subject. *A*, with no restriction of circulation. *B*, with venous outflow obstructed as in recording blood flow. The rise in limb volume from the beginning of one systole to the next indicates the volume of blood which would have flowed through the veins in that time; the fall in volume during diastole represents the outflow of blood retrogradely along the arteries.

Discussion

Individual measurements

LOCAL ARTERIAL PRESSURE. Winsor[4] has shown how the measurement of local arterial pressure can be usefully applied to the investigation of peripheral vascular disease. We have found that this measurement can be used to differentiate the segmental obstruction caused by an embolus, the localized obstruction of major arteries caused by atheroma, or the more wide-spread obstruction when medium-sized vessels are obstructed but the larger vessels are patent. In the occasional circumstances in which only one of two major vessels to a limb is obstructed, measurements of arterial pressure may fail to show the obstruction. Thus no reduction in systolic pressure at the ankle was found in a patient with intermittent claudication and a palpable dorsalis pedis pulse, although the volume pulse and the reactive hyperemia

in the calf were both reduced. In this case arteriography showed a block of the posterior tibial artery but no obstruction of the anterior tibial artery.

VOLUME PULSE The oscillometer,[9] oscillograph[10, 11] and the sectional plethysmograph have previously been used to record the volume pulse in the limbs. Burch[12] has fully described the hemodynamic and physiologic principles involved in the study of the volume pulse with particular reference to the digital circulation. The relationship between volume pulse and blood flow in the normal digit however differs from that in the more proximal parts of the limb. Burton[13] found a direct relationship between volume pulse and blood flow in the digit but we have been unable to demonstrate any relationship in the normal calf (Table I and Fig. 6). The discrepancy is probably due to the fact that an increase in blood flow in the normal digit is effected by opening up of arteriovenous anastomoses,[14] whereas an increase in blood flow in the forearm is believed to be achieved by the more general effect of

Table IV Systolic pressure, volume pulse and blood flow in the lower limb of a patient with thromboangiitis obliterans and atheroma before and after lumbar sympathectomy

	Upper thigh	Lower thigh	Calf	Ankle	Instep	Brachial blood pressure (acoustic)
Systolic pressure (mm. Hg)						
Before	110	0	0	60	+	130/90
After	125	90	60	55	+	140/90
Volume pulse (ml./100 ml./pulse)						
Before			Too small to be measured			
After			Too small to be measured			
Blood flow (ml./100 ml./min.)						
Before	+	3	2 8	3 7	3 0	
After	+	2 1	2 2	3 5	3 3	

Not measured

Table V Circulatory measurements in a case of polyarteritis nodosa before and after an extension of arterial obstruction

	Thigh	Calf	Ankle	Instep	Brachial artery
Systolic pressure (mm. Hg)					
Before	1	130	1	+	1 5/85
After	1?0	120	80	+	1 5/81
Volume pulse (ml./100 ml./pulse)					
Before	+	0 0?3	+	0 009	
After	+	0 017	+	0 007	
Blood flow (ml./100 ml./min.)					
Before	+	1 3	+	1 0	
After	+	1 1	+	0 3	

Table VI. Circulatory measurements in a patient with arteriosclerosis and left popliteal aneurysm

	Thigh	*Knee*	*Calf*	*Ankle*	*Instep*	*Brachial artery*
Systolic pressure (mm. Hg)						
Right	200	+	200	200	+	150/90
Left	200	+	200	200	+	+
Volume pulse (ml./100 ml./pulse)						
Right	0.020	0.018	0.025	0.027	0.024	
Left	0.029	0.056	0.070	0.016	0.014	
Blood flow (ml./100 ml./min.)						
Right	+	+	5.5	+	6.5	
Left	+	+	4.0	+	6.3	

[illegible]

relaxation of resistance vessels. We have found that no distinction could be made between normal subjects and patients with symptoms of arterial disease on the basis of blood flow in the resting calf, but measurements of volume pulse were distinctive. Thus no patients had a volume pulse greater than 0.03 ml./100 ml./pulse beat, whereas the volume pulse of normal subjects examined was greater than this (Fig. 6). In the past we and others[4] had disparaged oscillometric measurements in clinical medicine, so that the finding that a reduced volume pulse indicated a reduced *capacity for blood flow*, even when the resting blood flow was within normal limits, led us to inquire more closely into the factors affecting the volume pulse in the leg.

The volume pulse (Fig. 7,*A*) indicates the net balance of blood flowing into and out of the limb segment throughout the pulse cycle. Although the outflow is usually *thought of as occurring through the veins*, Shipley, Gregg and Schroeder[17] have shown that there may be considerable retrograde arterial flow toward the aorta during diastole. Hewlett and Van Zwaluwenburg[6] first remarked that if diastolic reduction of volume was still recorded in a plethysmographic tracing when the venous outflow was blocked, as during the recording of a blood flow curve, then it was difficult to escape the conclusion that retrograde arterial flow must be occurring. Such evidence of retrograde arterial flow is seen in Fig. 7,*B*, where the arterial outflow appears to exceed the venous outflow. The retrograde flow may be considered to be blood which would have passed through the tissues had the arterioles been sufficiently dilated to receive it. In this view, the amplitude of the systolic volume pulse in the limb gives an indication of the reserves of peripheral circulation. In accord with this view is the absence of evidence of retrograde flow when the arterioles are fully dilated, as is seen during measurement of blood flow by venous occlusion at the *height of reactive hyperemia*. *It is also* in accord with this view that relaxation of arterioles with vasodilatation in the limb should lead to a greater increase in blood flow than in volume pulse, whereas in the digits, where vasodilatation occurs by opening of arteriovenous anastomoses, the increases in volume pulse and blood flow are comparable.[14] The complexity of these changes is seen in the data given in Table I. When vasodilatation occurs by reflex heat, no significant change in blood flow[4] or volume pulse occurs in the calf; at the ankle the blood flow doubles but the volume pulse changes little; in the foot, where the effect of opening of arteriovenous anastomoses is appreciable, volume pulse does increase with vasodilatation but still to a lesser degree than does blood flow. The view that the volume pulse is a better indication than resting blood flow of *capacity*

for blood flow in a limb is also supported by the effects of restricting the reserves of peripheral circulation by arterial compression In the experiments shown in Fig 8 the brachial artery in the antecubital space was gradually occluded by screwing a padded G clamp down on it When the artery was partially occluded by this pressure blood flow was reduced only 10 to 15 per cent whereas the volume pulse was diminished by more than 80 per cent These experimental results reinforce our clinical observations that the volume pulse in the limbs is more sensitive to the effects of reduction of arterial caliber than is blood flow

When this study was started it was thought that the changes in the shape of the volume pulse curve i e a slower rising pulse or a delayed pulse might be of value in the recognition of the site and degree of obstruction These changes (Fig 4) have not added significantly to the information afforded by a simple measure of the amplitude of pulse volume

BLOOD FLOW In chronic arterial disease the development of collateral blood supply is usually sufficient to maintain a normal resting blood flow Except in severe ischemia and acute arterial obstruction therefore measurements of blood flow do not serve as a reliable indication of the vascular insufficiency unless extra demands are placed on the circulation as by a period of ischemia in the reactive hyperemia test or of muscular work in an exercise test

The clinical interpretation of measurements of blood flow in an exercise test may be difficult probably because we are not able to measure satisfactorily the blood flow to the muscles during the time that they are exercising The data in Fig 3 exemplify this difficulty In this patient with predominantly unilateral vascular disease the normal right leg showed the greater hyperemia *after* the vigorous exercise of hopping 60 times on each leg (Fig 3 *A*) although *after* the gentle exercise of walking 100 yards it showed the smaller hyperemia (Fig 3 *B*) Black [1] has shown that a normal circulation can keep pace with the blood flow required during mild exercise but when the severity of the exercise is increased a blood flow debt is incurred which is repaid during the subsequent hyperemia Therefore with mild exercise (Fig 3 *B*) the blood flow in the normal leg can keep pace with the small requirement but the inadequate circulation in the affected leg incurs a blood flow debt which must be repaid during the subsequent hyperemia During vigorous exercise (Fig 3 *A*) a metabolic debt is incurred in both legs but is more rapidly paid off in the normal leg

The adequacy of the circulation to meet increased demands may be more readily assessed by measurement of the hyperemia after a period of ischemia because the entire response can then be measured (Fig 3 *C*) Before operation the reactive hyperemia in this affected leg was considerably reduced but after surgical repair of the obstructed artery the reactive hyperemia became as great as in the healthy leg

Clinical application of measurements Commonly we assess the need for surgical treatment of arterial obstruction from the severity of the patient's symptoms and the state of nutrition of the tissues at the time the history is taken and the clinical exami

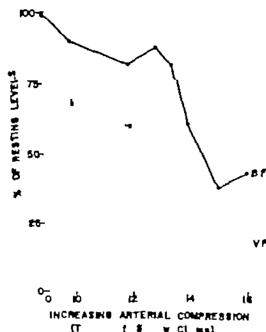


Fig 8 Effect on volume pulse and blood flow in the forearm when the brachial artery in the antecubital space ... subjected to gradually increasing compression

nation is made. The feasibility of arterial surgery is suggested when there is diminution or absence of pulsation in the femoral or popliteal arteries, because arterial grafting or thromboendarterectomy is technically possible only when the obstruction is in or above the popliteal artery. Valuable information in regard to the adequacy of the circulation to the feet is given by the results of a reflex heating test.[39] The usual practice is then to define the location and extent of the obstruction by means of arteriography or aortography before operation.

We make the measurements by strain gauge at some time between the clinical examination and the taking of the arteriogram. Measurements of the volume pulse and systolic pressure down the limb, as we have shown, can be used to localize any obstruction or series of obstructions which may be present, and so to indicate the level at which surgical treatment, whether it be arterial repair or amputation, may be undertaken. The volume pulse and pressure gradient also give an indication of the severity of the obstructions and the compensation afforded by the development of collateral circulation. If necessary, the capacity of the circulation to meet the increased demands can be measured by the results of a reactive hyperemia test.

Because the volume pulse and the pressure gradient in the thigh and calf are not greatly affected by changes in the state of warmth of the patient, investigation of them does not require a controlled temperature room and a wait for basal conditions. Thus the measurement by strain gauge could be added to the procedures used in the clinic to decide which patients should be admitted for arteriography. Because the equipment described can be quickly applied and does not inconvenience the patient, it can be used for repeated observations. Thus it is proving valuable in following the changes in the circulation over a prolonged period of observation.

This conclusion leads us to inquire whether equally useful information might not be obtained by simpler apparatus. It is pertinent to reconsider the use of an oscillometer of the Pachon or Collens type in place of the strain-gauge plethysmograph, for as customarily used such instruments give an indication of pulse volume. They can also be used to measure the systolic pressure at any level in the limb by inflating the cuff to above systolic pressure and then gradually reducing the pressure and noting the pressure at which oscillations are first seen. Sometimes the pulsations are so small that the volume pulse and systolic pressure cannot be measured in this way, but the smallness of the pulsation itself is an indication that there is a severe degree of arterial obstruction. We have not made a particular study of using the oscillometer in this way, and we should remind any reader who considers doing so that the cuff usually supplied is suitable for measurements of pressure in the arm, but that a wider cuff is required for satisfactory measurements in the leg.

Summary

The use of the mercury-in-rubber strain gauge to measure the circulation to the limbs is described. The instrument is quickly applied to the limb and can be used to make measurements of the circulation at many points on the limb. It has been used to measure blood flow, volume pulse, and systolic pressure at different levels on the limbs of normal subjects under various conditions and of patients with arterial disease. The range of these measurements in the legs of normal subjects is defined.

The measurement of the systolic pressure gradient down the limb also gives a good indication of the location and degree of arterial obstruction or obstructions.

The amplitude of volume pulse has been found to be a better indication of the location and severity of chronic arterial obstruction than are measurements of blood flow. This finding led to a consideration of the relationship between blood flow and amplitude of the volume pulse. An argument is put forward for considering the volume pulse as an indication of the degree of reserve of the peripheral circulation.

The clinical application of the results in the selection of patients for arterial surgery is considered, and means are suggested by which an oscillometer could be used to

provide information on the location and severity of obstruction of the larger arteries

W e h t thank M George Ferce and M H n Neville for ass tance in setting up the tra gauge apparatus

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The effect of ammonium chloride and sodium bicarbonate on the urinary excretion of magnesium, calcium, and phosphate

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Relatively few studies have been made in the control subject on the effect of ammonium chloride or sodium bicarbonate on the urinary excretion of magnesium calcium and phosphate This paper reports such a study in 6 control subjects

I Material and methods

Six healthy ambulatory subjects who were between the ages of 23 and 37 years and who ranged in weight between 112 and 190 pounds participated in the study (3 male medical students 1 female medical student 1 medical student wife and 1 female laboratory technician) They thoroughly understood the importance of the test as to careful 24-hour collections of urine and diet control These subjects ate the same self selected diet for the 3 periods of 5 days each of the experiment and collected 24 hour samples of urine during the same period No preservative was added to the urine when the subjects were taking ammonium chloride Thymol was used as a preservative during the control period and when sodium bicarbonate was taken Samples of blood were drawn on the third day of each 5-day period The 3 periods of study were as follows and in the sequence listed except in one subject (R J) in whom period 1 and 2 were reversed (1) control diet—5 days (2) control diet plus 8 Gm of $NaHCO_3$ (95 2 mEq of sodium) daily—5 days (3) control diet plus 8 Gm of NH_4Cl (plain) (151 2 mEq of calcium) daily—5 days During the 2 days or more in a few instances between periods the subject ate any diet desired

Levels of serum magnesium were determined by the method of Simonsen and associates and magnesium in the urine by a modification of this method serum and urinary calcium by the method of Clark and Collip and serum and urinary phosphate by the method of Simonsen and associates[2] Levels of serum bicarbonate were determined by the Van Slyke titration method Urine pH was determined by the Beckman pH meter

II Results

The urine of all subjects was made more acid (pH 4 8-4 9) and the levels of serum bicarbonate fell below control values during ingestion of ammonium chloride During the ingestion of sodium bicarbonate the urine pH became more alkaline (7 2 8 3) and there was a slight rise in the level of serum bicarbonate in all but one subject

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Table I. Effect of NH_4Cl on urinary excretion of magnesium, calcium, and phosphate

Subject, sex, age	Magnesium: Control period (mEq./5 days)	Magnesium: NH_4Cl period (mEq./5 days)	Magnesium: Difference (mEq.)	Calcium: Control period (mEq./5 days)	Calcium: NH_4Cl period (mEq./5 days)	Calcium: Difference (mEq.)	Phosphate: Control period (mM/5 days)	Phosphate: NH_4Cl period (mM/5 days)	Phosphate: Difference (mM)
J. A. M 24	52.54	58.71	+6.17	45.77	70.11	+24.34	147.8	165.8	+18
E. W. M 23	85.45	91.00	+5.55	67.41	85.26	+17.85	207.6	198.7	−8.9
D. H. M 31	53.19	56.40	+3.21	76.25	101.56	+ 5.31	145.45	160.1	+14.65
S. H. F 28	33.05	35.01	+1.96	32.35	58.85	+26.50	115.41	132.95	+17.54
L. M. F 30	40.96	46.08	+5.12	43.52	61.3	+17.78	114.05	138.2	+24.15
R. J. F 37	26.80	34.75	+7.95	24.30	49.7	+ 5.40	113.0	156.9	+43.9
Mean			+4.99 ± 0.87† $p < .01 > .001$			+22.86 ± 3.1† $p < .01 > .001$			+18.2 ± 6.9† $p \approx .05$

*Eight grams of NH_4Cl per day by mouth.
†Standard error of the mean.

Table II. Effect of $NaHCO_3$ on urinary excretion of magnesium, calcium, and phosphate

Subject*	Magnesium: Control period (mEq./5 days)	Magnesium: $NaHCO_3$† period (mEq./5 days)	Magnesium: Difference (mEq.)	Calcium: Control period (mEq./5 days)	Calcium: $NaHCO_3$† period (mEq./5 days)	Calcium: Difference (mEq.)	Phosphate: Control period (mM/5 days)	Phosphate: $NaHCO_3$† period (mM/5 days)	Phosphate: Difference (mM)
J. A.	52.54	47.47	−5.07	45.77	42.9	−2.82	147.8	130.9	−16.9
E. W.	85.45	79.66	−5.79	67.41	62.75	−4.66	207.6	194.3	−13.3
D. H.	53.19	54.76	+1.57	76.25	70.10	−6.15	145.45	116.9	−28.55
S. H.	33.05	29.52	−3.53	32.35	28.46	−3.89	115.41	97.3	−18.11
L. M.	40.96	35.87	−5.09	43.52	41.40	−2.12	114.05	117.23	+3.18
R. J.	26.80	29.7	+2.90	24.3	20.3	−4.0	113.0	103.8	−9.2
Mean			−2.5 ± 1.5‡ $p < .2 > .1$			−3.81 ± 0.64‡ $p < .01 > .001$			−13.8 ± 4.3‡ $p < .05 > .02$

*See Table I for age and sex.
†Eight grams of $NaHCO_3$ per day by mouth.
‡Standard error of the mean.

above the control levels but not above the normal for this determination.

Table I documents the effect of ingestion of 8 Gm. of ammonium chloride per day for 5 days on the urinary excretion of magnesium, calcium, and phosphate in each subject as compared to the control period. The range of urinary electrolyte excretion of the different subjects is seen to vary widely in the control period. Despite this there was a mean increase in urinary magnesium (+4.99 mEq.), calcium (+22.86 mEq.), and phosphate (+18.2 mEq.) which was statistically significant during ingestion of ammonium chloride.

Table II gives the results of ingestion of sodium bicarbonate on the urinary excretion of these same ions. Four of

Table III. Review of changes in urinary electrolyte excretion with ingestion of NH_4Cl (from the literature)

Investigator and Year	Number of Subjects	NH_4Cl (Gm.)	Increase over control electrolyte excretion: Ca (mEq.)	Mg (mEq.)	PO_4 (mM.)	Type of Comparison
Wiley et al 1933	1	5 2	22	8	14	Total increase during 6 days on NH_4Cl over 6 days of control period
Talbott and Stub 1937	1	12 18	7	8 3		Total increase during 6 days on NH_4Cl over 6 days of control period
	1	12 18	28	48	27	
Martin et al (This study 1959)	6	8	22 86	4 99	18 2	Total increase (mean for group) during 5 days on NH_4Cl over 5 days of control period
Keith et al 1926	1	10 5	5 5	1 7	3	1 day on control—3 days on NH_4Cl. Figures given are maximum 24 hour increase while on NH_4Cl
Sartorius and [illegible] 1949	1	15	23 8	3 7		Maximum 24 hour increase on NH_4Cl over mean 24 hour excretion of 5-day control period
	1	10 5			19	
Martin et al (This study 1959)	6	8	7 11†	3 45†	8 37†	Maximum 24 hour increase in electrolyte excretion on NH_4Cl over mean 24 hour excretion of 5-day control period (mean for group)*

* Recomputed from tabulated [illegible] results
† All [illegible] significant [illegible]

subject showed a decrease in urinary excretion of magnesium whereas 2 showed a rise as compared to the control period. The mean change was not statistically significant. All subjects showed a decrease in the urinary excretion of calcium with a mean decrease of 3.8 mEq., which was a significant mean change. All but one subject showed a decrease in urinary excretion of phosphate but the mean decrease was not highly significant.

No significant changes in the values for serum magnesium or calcium as determined on the third day of each test period were found. Some minor to moderate variations in the levels of serum phosphate occurred in a few subjects but without any definite pattern.

Discussion

Presumably healthy subjects are in magnesium, calcium and phosphate balance and excrete any excess of these ions ingested. If each subject ate the same diet in each of the test periods, although different for each subject, changes in the excretion of electrolyte should represent the effect of the drug taken and not the amount of dietary electrolyte.

Thus this project was designed to see not only whether there were changes in the urinary excretion of magnesium, calcium and phosphate after ingestion of ammonium chloride or sodium bicarbonate but whether there was an average or mean response to these drugs despite variation of age, sex, weight and intake of electrolytes. This was done purposely since acidifying or alkalinizing agents are given to patients of different age, sex and weight and on diets which differ as to the content of magnesium, calcium and phosphate.

The results clearly show an increased urinary excretion of magnesium, calcium and phosphate in all subjects after acidifica-

tion of the urine with ammonium chloride Furthermore there was a mean response for the group which was statistically significant despite variations in sex weight age and urinary output of electrolytes during the control period

Only four studies (6 control subjects) have previously been reported[4,5] on the effect of ammonium chloride on the urinary excretion of magnesium calcium and phosphate Table III summarizes this data The material from the literature where possible has been rearranged and recalculated to compare with our data although amounts of ammonium chloride and periods of study were not always similar Increases in the urinary output of magnesium calcium and phosphate during therapy with ammonium chloride was shown in all studies The amount of these increases varied from our results in some instances In part this may be due to differences in the amount of drug used and the period and design of the study

Jabir and associates reported acute increases in the excretion of magnesium after ingestion of ammonium chloride but the design of his experiment does not allow comparison with our results

Although the effects of acidifying salts on the excretion of calcium is well known little attention has been paid to their effect on excretion of magnesium in urine

Previous studies from our laboratory have shown a fall in the level of serum magnesium and marked increases in the output of magnesium in the urine in patients with congestive heart failure who were receiving prolonged diuretic treatment with ammonium chloride and Mercuhydrin The present study documents increased urinary output of magnesium in control subjects after the administration of ammonium chloride The possibility of depletion of body magnesium with repeated and prolonged use of ammonium chloride particularly if the dietary intake of magnesium is low is thus a possibility particularly if more potent diuretics such as the mercurials or chlorothiazide follow the use of ammonium chloride The effects of depletion of magnesium in the experimental animal are well known The studies of Flink[11] have delineated the clinical picture of magnesium deficiency —

Only one other study in one subject[5] has dealt with the effect of sodium bicarbonate on the urinary excretion of magnesium calcium and phosphate In this study changes in urinary electrolytes during 6 days of ingestion of 100 mEq of NaHCO over a 6-day control period were as follows decrease in calcium of 7 5 mEq increase in magnesium of 7 mEq increase in phosphate of 1 mM Ingestion of sodium bicarbonate in our study caused a decreased urinary excretion of magnesium in 4 subjects of calcium in 6 subjects and of phosphate in 5 subjects The mean change was highly significant only for calcium (−3 81 mEq)

Summary

Six normal subjects showed mean or average increases which were statistically significant in urinary output of magnesium (+4 99 mEq) calcium (+22 86 mEq) and phosphate (+18 2 mM) during 5 days of ingestion of ammonium chloride as compared to a 5-day control period This occurred despite differences in the intake of electrolytes age sex or weight The possible significance of the loss of magnesium during diuretic therapy was discussed

During ingestion of sodium bicarbonate there was a mean decrease over the control period which was statistically significant only for urinary output of calcium (−3 81 mEq)

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Experimental and laboratory reports

Supernormal phase of atrioventricular (A-V) conduction due to potassium
A-V alternans with first-degree A-V block

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In an earlier report dealing with the effect of potassium on A-V conduction in dogs a brief reference was made to the fact that a supernormal phase of A-V conduction was observed with remarkable regularity. It seems to us that this observation in an intact mammal under experimental conditions bridges the gap between the demonstration of the supernormal phase in isolated myocardium on one hand and the existence of this phenomenon in the human heart on the other hand. To the best of our knowledge the phase of supernormal A-V conduction has not been demonstrated under any circumstances in an intact mammal other than man. The failure to register this phenomenon is especially surprising in view of the extensive studies involving potassium and its relation to the heart.

Supernormal phase, or rather relative supernormal phase of recovery of excitability, first discovered by Adrian and Lucas[2] in 1912 in nerve tissue and later described for the cardiac muscle by Adrian, refers to a period in the recovery of excitable tissue during which the response to a stimulus is exaggerated. A supernormal phase of A-V conduction was described by Ashman in compressed turtle heart. Lewis and Master[4] were unable to confirm the existence of supernormal conduction in cardiac tissue of the dog. Commenting on the failure to find the exaggerated phase of response in a mammalian heart other than the human, Ashman and Herrmann wrote in 1926: "A supernormal phase in conduction has not yet been described for the mammalian heart other than that of man, but we are convinced that it will be demonstrated experimentally in the mammal when the right conditions are obtained, for it is a phenomenon manifested by the excitability, contractibility, or conductivity of such diverse tissues as nerve fibers, skeletal muscle, and cardiac muscle, both auricular and ventricular."

In 1947 Mack and Langendorf, in a critical review of clinical cases reported to that date, again noted the failure to reproduce the supernormal phase experimentally in the mammal. They stated: "Since partial A-V block is not uncommon and yet genuine instances of supernormal phase of recovery are seen to be extremely rare, it is not surprising that the supernormal phase of recovery of conductivity could not be found in the mammalian

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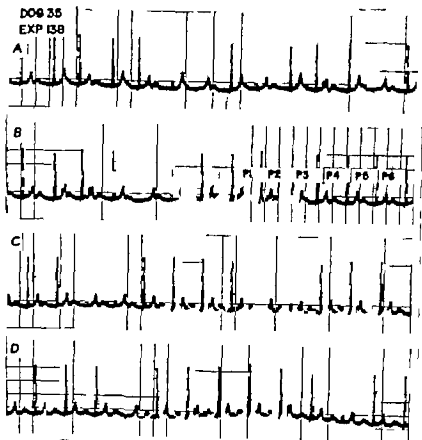


Fig. 1. A continuous tracing showing gradual transition of A-V alternans to regular A-V conduction. Note the sudden shortening of P-R following P5 in strip *B*. For details see text.

heart experimentally. They do not agree that failure to observe this phenomenon *in the laboratory necessarily denies its* existence in man.

Although supernormal A-V conduction was observed with all degrees of A-V block, we will confine our presentation to A-V alternans as a manifestation of supernormality. The purpose of this presentation is to (1) describe the electrocardiographic findings in greater detail, (2) present a differential diagnosis of other conditions which could simulate supernormal conduction in our recordings, and (3) discuss the possible relationship of potassium to the phenomenon of supernormal conduction in depressed and fatigued hearts.

The supernormal conduction in our animals is shown by criteria outlined by Ashman and Herrmann, which may be restated in electrocardiographic terminology as (1) the sequence of short R-P *followed* by short P-R and a long R-R by a longer P-R and (2) the transmission of an impulse *after an R-P, the latter if shortened or* prolonged would result in a completely blocked P wave.

Method

Mongrel dogs which weighed 9 to 15 kilograms were used in these experiments. The animals were anesthetized with 30 mg. of sodium pentobarbital per kilogram of body weight and given intravenous potassium in the form of isotonic solution *of buffered potassium phosphate in dis*tilled water at a rate of 1.0 to 1.2 mEq per minute. The uniform rate of infusion was assured through the use of the flowmeter. In some the injection of potassium was preceded by the administration of acetyl strophanthidin (Lilly) or rarely digitoxin and in some experiments po*tassium alone was given.* The acetyl stro

phanthidin was administered at a rate of 0.06 mg every 30 seconds until an arrhythmia appeared. Digitoxin when used was given at an average dose of 0.4 mg per kilogram of body weight. Each experiment was monitored with an oscilloscope and when advisable permanent recordings were made using standard lead II connections.

Unless otherwise indicated the R-P and P-R intervals are measured from the respective Q wave to the summit of P wave and in the case of the ventricular cycle from Q to Q. On occasions the P waves will be fused with the preceding T wave and an unavoidable error in measurements is likely to occur. Because of a basically regular P-P interval this error is minimal and in no way invalidates our interpretation.

Description of electrocardiograms

Supernormal conduction in the form of A-V alternans when specifically searched for was recorded in nearly all of the experiments regardless of whether the potassium was preceded by infusion of cardiac glycosides or not.

Fig. 1 (*Dog 3, Exp. 135*). This is a continuous tracing recorded after administration of 0.96 mEq of acetyl strophanthidin and 10.5 mEq of potassium phosphate. The plasma level of potassium at

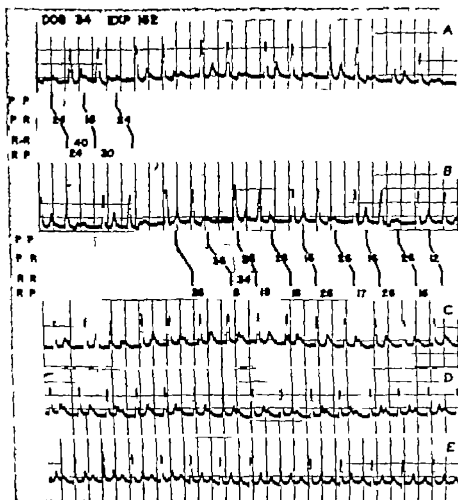


Fig. 2. A continuous tracing showing A-V alternans and delayed intraventricular conduction with gradual disappearance of alternans of A-V conduction and ventricular aberration. Note the irregular coupling of the ventricular complexes and the gradual emergence of regular ventricular rhythm with fixed P-R. Such behavior would be most unusual for ectopic beats. For details see text.

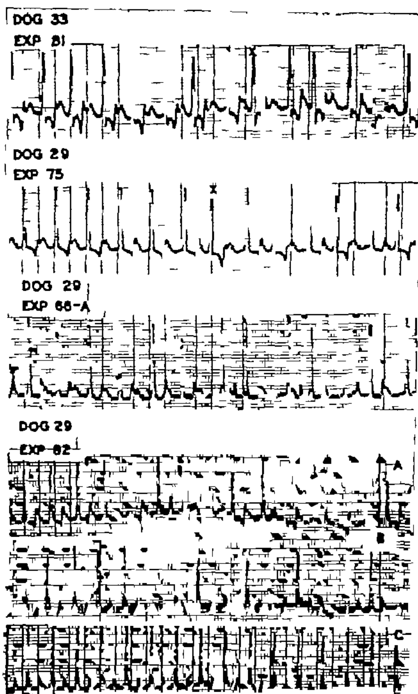


Fig. 3. This is a composite of three separate experimental tracings, *A*, *B*, *C* in Exp. 82 being continuous, and demonstrates the relation of aberrancy of ventricular complex to the antecedent recovery period as well as to the immediately preceding cardiac cycle. As long as the R-R interval varies little the QRS complexes have an almost uniform appearance. For details see text.

the time this tracing was obtained was 8.0 mEq./L. This tracing reveals a regular sinus rhythm with a P-P of 0.48 second (rate 130 per minute) with a varying P-R interval. General inspection of the tracing discloses A-V alternans which begins in strip *A* and which can still be detected through the fifth QRS complex

in strip *C*. The unusual feature of A-V conduction is the paradoxical behavior of P-R in relation to the preceding R-P. Normally the shorter R-P intervals are followed by longer P-R and longer R-P by shorter P-R. In this instance the reverse is the case. The first P-R in strip *A* measures 0.22 second and is preceded by a R-P of 0.26 second, whereas the next R-P in the same strip, although measuring only 0.20 second, is followed by a P-R of only 0.16 second. The respective R-R intervals measure 0.44 and 0.39 second. The paradoxical alternans of the A-V conduction interval continues but, as expected, becomes less pronounced as the R-P becomes longer and the atrial impulse falls in a relatively less refractory period until the difference is only 0.02 second (between the first and second P-R intervals in strip *C*). The alternans can no longer be detected with means at our disposal after the sixth complex of strip *C*. At that time the R-P and P-R measure 0.28 and 0.15 second respectively, with the P-R gradually shortening until it measures 0.12 second in strip *D*.

In strip *B* a sequence of P waves was arbitrarily numbered from 1 to 6. The interesting feature in this group of complexes is a rather pronounced shortening of P-R following P3. With the beginning of strip *B* the alternans is quite obvious, the difference between the longer and shorter R-P is about 0.04-0.05 second. This variation becomes gradually less pronounced until the difference between R-P1 (0.23 second) and R-P2 (0.24 second) is only 0.01-0.02 second. The P2-R (0.23 second) is longer than one would anticipate from inspection of the preceding cycles. As a consequence of the P-P interval remaining regular the R-P3 is suddenly shortened (0.21 second) and is followed by a paradoxically short P3-R (0.14 second). The latter is shorter than any in strip *B* and almost as brief as any seen in this tracing. The sudden change of P3-R can be explained only by supernormal conduction.

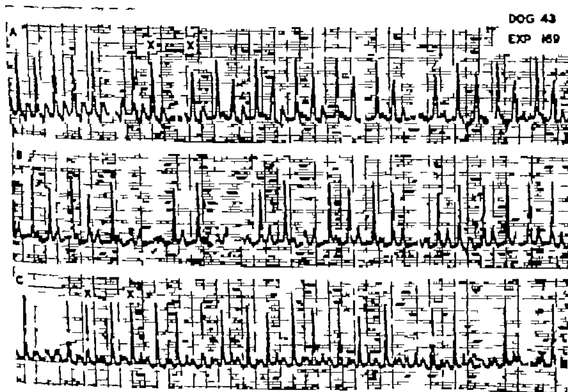


Fig. 4. This tracing demonstrates the paradoxical behavior of A-V conduction and the dependency of ventricular aberrancy on the duration of the immediately preceding recovery period as well as antecedent ventricular cycle. The aberrant conduction ceases as the R-P cycle becomes more regular.



Fig. 5. A continuous tracing showing effect of superimposed conduction manifested by A-V alternans, appearance of second-degree A-V block, and resumption of 1:1 conduction after infusion of potassium was stopped. Portions of the tracings are reproduced in Fig. 6.

Fig. 2 (Dog 31, Exp. 162). This is a continuous tracing recorded after administration of 0.96 mg. of acetyl strophanthidin and 11.6 mEq. of potassium phosphate. The plasma level of potassium at the time of recording was 6.5 mEq./L. This electrocardiogram shows a sinus rhythm with a regular P-P interval of 0.44 second and varying P-R interval. A-V alternans is obvious with shorter R-P followed by shorter P-R and longer R-P by longer P-R. The alternans becomes less pronounced as the R-P lengthens and can no longer be detected in strip *I*. The shorter of the two ventricular cycles (R-R) varies from 0.40 second between the first and second QRS complexes in strip *A* to 0.34 second between the seventh and eighth QRS complexes in strip *B*. There is little if any difference in the appearance of QRS complexes after either the longer or shorter R-R interval, but there is a gradual narrowing of all the ventricular complexes as well as shortening of P-R from the beginning of the tracing (strip *A*) to the end of strip *I*. Such rapid change of

intraventricular and atrioventricular conduction were frequently seen when infusion of potassium was stopped.

Fig. 3. The sections of cardiograms, all of which show regular sinoatrial rhythm and 1:1 with delayed A-V conduction, are shown to emphasize the point that the aberrant QRS complexes giving rise to QRS alternans appear not only as the distance from the aberrant QRS to preceding QRS shortens but also follow a longer immediately preceding cycle. The importance of this relation to the preceding R-R in the differential diagnosis of supernormal conduction from ectopic beats will be pointed out below.

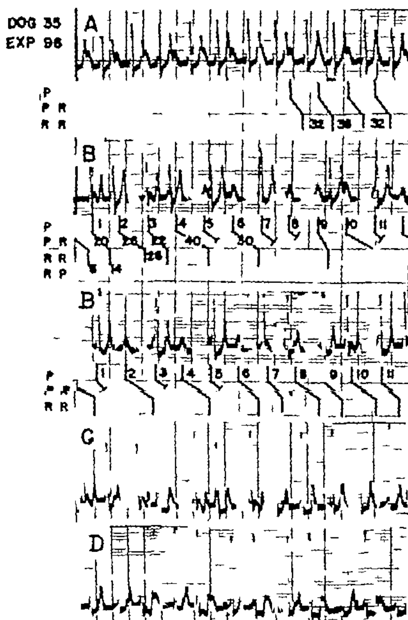


Fig. 4. This figure represents portion of the tracing of Fig. 5 and allows for more detailed study of the A-V alternans and the onset and termination of second-degree A-V block. Note the marked variation in coupling from strip *A* to strip *D* as well as disappearance of the aberration of QRS toward the end of strip *C* when the R-R distance becomes regular.

Dog 33 (Exp. 81). This tracing was recorded after administration of acetyl strophanthidin and while potassium was being infused. At the time this cardiogram was obtained a total of 16.5 mEq. of potassium was administered and the plasma level of the cation was 9.4 mEq./L. A-V alternans is present in the entire strip but becomes clearer after the seventh QRS complex. There is some slight variation in the QRS beginning with the third ventricular complex, but the aberrancy is manifested largely by alternation in the height of the QRS complex and deepening of the S wave after a sudden prolongation of the cycle immediately preceding the ninth ventricular complex (x). An identical situation is shown in the tracing obtained on Dog 29 (Exp. 66-A) given 15 mEq. of potassium 24 hours after administration of 5.0 mg. of digitoxin. The case of Dog 29 (Exp. 75) differs from the foregoing experiment in that this animal was given potassium only. A-V alternans becomes obvious after the third ventricular complex. Comments regarding QRS alternans and aberrancy and their relation to the duration of the preceding cycle made above apply equally well in this instance.

Strips *A*, *B*, and *C* recorded in Dog 29 (Exp. 82) represent a continuous tracing. In this experiment only potassium in the amount of 10 mEq. was given, and at the time this tracing was recorded the plasma level was 7.4 mEq./L. QRS aberration and ventricular alternans follow a sudden prolongation of the R-R interval between the fifth and sixth ventricular complexes in strip *A*. This prolongation of R-R was due to a longer P-R which paradoxically followed a longer R-P. This now longer R-R cycle is followed by short R-P, short P-R, terminating with an aberrant QRS (x). The paradoxical A-V alternans persists in strip *B*. As the alternans of A-V conduction gradually ceases, the R-R intervals become regular and the aberrancy of QRS disappears (strip *C*).

Fig. 4 (Dog 43, Exp. 169). This animal was given potassium only. Strip *A* was recorded toward the end of the infusion, and strips *B* and *C* were recorded 1 and 2 minutes after the end of the infusion, respectively.

In strips *A* and *C*, aberrant ventricular complexes (x) become obvious when the aberrant QRS is closer to the last ventricular complex and when it follows an immediately preceding longer R-R cycle. The absence of QRS aberration is noted at the beginning of strips *A* and *C* and at the end of strips *B* and *C* when the R-R intervals show little or no variation. This cardiogram again serves to point out that the aberrancy is dependent on the distance from the last ventricular complex as well as the duration of the immediately preceding cardiac cycle. It is important to note that the aberrant complexes have no fixed relation to preceding QRS, and that the degree of aberration varies with the alternans of R-R interval, disappearing gradually as the R-R periods become more or less equal. These observations rule out ectopic bigeminy with the possible exception of a very unlikely situation of irregularly coupled nodal or septal ventricular premature systoles with varying degree of aberration and appearing only after shorter R-P.

Fig. 5 (Dog 35, Exp. 96). This dog received 5.0 mg. of digitoxin 48 hours before the infusion of potassium. The tracing shown in this figure was recorded after injection of 4.8 mEq. of potassium preceded by administration of 0.72 mg. of acetyl strophanthidin. At the time the tracing, which is a continuous recording, was registered the plasma level of potassium was 6.5 mEq./L. The figures in the left upper corner indicate the time in seconds from the beginning of the recording. Portions of this tracing marked *A*, *B*, *B'*, *C*, and *D* are reproduced and analyzed in greater detail in Fig. 6. The part marked *B* includes the first four ventricular complexes from 36 second strips. The distance between the P waves is regular, measuring 0.36 second. This tracing represents a complete sequence beginning with appearance of alternans of A-V conduction (top and 9 second strips) as the plasma potassium was rising, and development of second degree heart block, at which point infusion of potassium was stopped and 1:1 A-V response with paradoxical alternans of A-V conduction reappeared. The latter becomes progressively less pronounced until it is hardly discernible in the 72 second strip.

Fig. 6 (Dog 35, Exp. 96). This figure

represents sections of the continuous tracing reproduced in Fig 5 and allows for better presentation of detail Strips *A* and *C* merely show the paradoxical behavior of P R in relation not only to its respective R P but also to the preceding R R cycle Strip *A* was obtained as the plasma potassium was rising and strips *C* and *D* as the level was falling Strips *B* and *B'* which are continuous show the beginning of second degree heart block with failure of P5 in strip *B* to conduct It is possible but not very likely that P5 is responsible for the sixth QRS The block is 2 1 except in strip *B'* in which P7 8 9 are paired with only one QRS giving rise to a 3 1 block There is little doubt that P2 4 and 6 in strip *B'* initiate the second third and fourth ventricular complexes respectively

Comment

The paradoxical behavior of P R in relation to preceding R P for reasons already mentioned can be explained best by a supernormal phase of conduction This interpretation is strengthened by the fact that the shorter P R follow not only shorter R P but also an immediately preceding longer R R cycle Ordinarily the refractory period varied directly with the preceding R R cycle and the finding that a shorter R P following a longer R R is accompanied by a shortened P R is most unexpected and further supports the existence of supernormal conduction Although A V conduction during the supernormal phase was shorter than either in the preceding or succeeding cycle in no instance was the P R shorter than the control P R thus the term relative supernormal period reflects better the actual nature of accelerated conduction under discussion This is in keeping with findings in human subjects in whom the supernormal phase was always accompanied by pronounced depression of A V conduction

For reasons already outlined it is unlikely that the R R alternans is due to ectopic beats Other mechanisms such as the heart rate fatigue phenomenon possible change in intensity of atrial impulse concealed conduction and finally A V dissociation with interference could not explain the paradoxical behavior of A V conduction observed in these experiments The existence of a dual A V transmission pathway has been offered as an explanation for A V alternans The various mechanisms which may result in A V alternans are summarized by Langendorf The variation in position of the supernormal phase was observed earlier[7] and was explained variously by change in tone of extracardiac nerves and fluctuation in A V conductivity

Adrian and Lucas observed that the main functions of living tissue namely excitability conductivity and contractility all increased above their normal value when the tissue was perfused with acid medium Subsequently Adrian pointed out that at a pH of 3 0 the conduction became suspended completely but that up to that point the supernormal conduction became progressively more marked Since acidosis results in loss of the cellular potassium and causes a concomitant increase of extracellular potassium it is attractive in light of our findings to speculate that the rising level of potassium is at least partially responsible for the appearance of supernormality Our animals behaved in a fashion somewhat similar to Adrian s preparations As Adrian lowered the pH the supernormal conduction became more marked until at a pH of 3 the conduction became suspended Similarly as we increased the plasma levels of potassium the supernormal phase was observed after a progressively shorter recovery period (R P) Indirect support for the concept that potassium may be the common denominator responsible for the appearance of supernormal phase comes from the observations that depression of A V conduction a prerequisite for appearance of supernormality due to anoxia fatigue injury and perhaps vagal effect is associated with a rise in extracellular potassium [12,13] The exact manner in which the cation results in recordable supernormal conduction is obscure It is unlikely however that this phenomenon can be accounted for either by a shortening of the action potential or by a lowering of the resting membrane potential which accompanies the rise of plasma potassium because such changes would not explain the rapid variation of conduction from cycle to cycle

Summary

1 Supernorm il ph ise of A V conduction was recorded for the first time under experimental conditions in an intact m im mil (dog) Potassium was the agent re sponsible for depression of A V conduction and appe ir ince of supernorm il conduction

2 This observ ition bridges the gap between the previously described super normal ph ise in compressed and f itigued he irt muscle prep ir ition on one h ind and in the hum in he irt on the other hand and supports strongly the existence of supernormal ph ise of A V conduction in the clinic illy reported cases

W wish t thank Dr Richard Langendorf nd Dr Alfred I k for review ng much of the mat ri l dealing with A V lterm

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Reactivity of the digital blood vessels to angiotensin II in normotensive and hypertensive subjects

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The reactivity of digital blood vessels to l-norepinephrine has been found to be increased in essential hypertension and in Cushing's syndrome whether spontaneous or produced artificially by the administration of glucocorticosteroids. Administration of glucocorticosteroids, however, increases this reactivity in normotensive but not in hypertensive subjects,[1] and sodium depletion decreases reactivity in hypertensive subjects but increases it in normotensive subjects. These facts suggest that the increased reactivity of vascular smooth muscle in essential hypertension, which may be a cause of the disease, is on a chemical basis involving either the chemical substances responsible for binding or degradation of the catecholamines or those responsible for contraction of smooth muscle itself. It was of interest, therefore, to study the reactivity of digital blood vessels to angiotensin II. This substance is a polypeptide and quite different in structure from the catecholamines.

Methods

Fifteen normotensive subjects and 15 patients with essential or primary hypertension were tested. Each subject was studied under three sets of conditions: (1) supine at rest under standardized conditions (room temperature 26-29°C.) (Phase B); (2) after indirect heating for at least half an hour with a cradle baker over the trunk until positive heat balance as manifested by profuse diaphoresis was achieved, followed by the intravenous injection of 0.5 mg. per Kg. of 2,6-dimethyl-1,1-diethyl piperidinium bromide (SC 1950) (Phase A); (3) after, in addition to the procedures in Phase A, infusing sufficient angiotensin II and additional SC 1950 to bring the level of blood pressure to its prior value or somewhat above it (Phase C). The concentrations in the infused fluid were glucose 50 mg. per c.c., angiotensin II 12 μg. per c.c., and SC 1950 0.09 mg. per c.c. The rate of infusion was regulated with an infusion pump. Studies were not performed until the level of blood pressure was stable.

Although the techniques have been presented in detail in previous communications,[4] some aspects of the method will be briefly reviewed. Flow in the digit is measured calorimetrically, and both systolic and diastolic arterial pressures are measured with a Gaertner capsule. These pressures are converted to mean pressure by adding one third of the pulse pressure to the diastolic pressure. A calculated venous pressure correction factor is sub-

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Table I. Statistical analysis of digital circulatory studies: reactivity to infused angiotensin II (AT)

	Phase	15 Normotensive subjects Mean ± SD	15 Hypertensive subjects Mean ± SD
Brachial blood pressure, systolic (mm Hg)	A	111 ± 11	135 ± 26
	B	115 ± 11	188 ± 32
	C	141 ± 15	209 ± 32
Brachial blood pressure, diastolic (mm Hg)	A	61 ± 8	87 ± 13
	B	70 ± 6	108 ± 12
	C	92 ± 10	126 ± 13
Digital blood pressure, systolic (mm Hg)	A	92 ± 10	121 ± 26
	B	101 ± 4	172 ± 29
	C	124 ± 13	183 ± 33
Digital blood pressure, diastolic (mm Hg)	A	54 ± 6	76 ± 12
	B	59 ± 8	102 ± 14
	C	73 ± 10	113 ± 14
Effective mean digital blood pressure (mm Hg)	A	56 ± 6	81 ± 16
	B	68 ± 9	120 ± 17
	C	83 ± 6	126 ± 17
Radius equivalent (10- cm)	A	3.0 ± 0.21	2.8 ± 0.19
	B	2.5 ± 0.39	2.2 ± 0.63
	C	2.9 ± 0.26	2.5 ± 0.22
Digital blood flow (cm /cm skin/min)	A	0.26 ± 0.023	0.26 ± 0.063
	B	0.12 ± 0.023	0.13 ± 0.058
	C	0.27 ± 0.024	0.26 ± 0.085
Work of vasoconstriction (10³ ergs)	B	2.4 ± 2.8	3.4 ± 3.1
	C	0.62 ± 0.29	1.5 ± 0.93
Rate of AT infusion (μg/min)	C	1.9 ± 0.74	1.1 ± 0.37
Work of vasoconstriction per μg AT per minute (10⁴ ergs)	C	0.35 ± 0.13	1.4 ± 0.68

*Standard error of d.f. ... = 0.18; p < ...
A: After ... B: Before ... C: After ... AT

tracted from the mean pressure. The radius equivalent of the circulation in the dilated state (Phase A) is calculated from the flow and effective mean pressure by using Poiseuille's law. A calculated length factor is considered to be constant for the digital circulation, correction being made for variation in the size of the finger tip. In both the resting-constricted and in the angiotensin II-constricted phases of the procedure (Phases B and C) the mean digital arterial pressure is determined as indicated for Phase A. The venous pressure correction factor and the pressure axis intercept for that grade of vasoconstriction is calculated are subtracted from the mean pressure. The latter correction incorporates the factors of critical closing pressure and/or apparent viscosity as influenced by the degree of vasoconstriction. The radius equivalent of the digital vessels in the constricted state is calculated from the corrected effective mean pressure and flow during vasoconstriction by using Poiseuille's law. The

length factor is again assumed to be unchanged. From the pressures and the change in radius equivalent the force and work of vasoconstriction can be estimated and from the work and infusion rate the work per microgram of angiotensin II infused per minute is calculated. The formula used for calculating work of vasoconstriction[9] is

$$w = 197P\ (r_1 - r\ ) - \frac{16.1P}{Q_1}\ (r\ \ - r\ ^4)$$

in which w is work in ergs, P is effective mean pressure, Q_1 is blood flow, and r is radius equivalent during vasodilatation whereas r is radius equivalent during vasoconstriction.

Results

The results are presented in Table I and Fig. 1. It is clear that the patient with essential hypertension is more reactive to angiotensin II than is the normotensive subject. The magnitude of the difference is about the same as for reactivity to l-norepinephrine. The difference can be demonstrated to be significant in terms of resistance as well as work of vasoconstriction. It is also apparent that angiotensin II is about 10 times as vasoconstrictive milligram for milligram as is l-norepinephrine in both the normotensive and hypertensive subject.

Discussion

That increased reactivity is a generalized phenomenon in essential hypertension rather that one localized to the digit is evident from the results of the cold pressor test[8] and from the fact that reactivity of systemic[9] and forearm blood vessels to l-norepinephrine and to angiotensin II has been found to be increased in essential hypertension. It is also apparent that this represents vascular smooth muscle rather than nervous reactivity since the effect is brought out after sympathetic neural blockade. It is probably not a manifestation of structural changes in the blood vessel wall such as hypertrophy of smooth muscle or intimal proliferation,[1] since reactivity to l-norepinephrine is increased early in the course of essential hypertension[11] and is normal in Raynaud's disease[1] and in renal hypertension.[7] If a deficit in catechol-O-methyl transferase is involved in this phenomenon this enzyme would have to be considerably less specific than hitherto postulated. On the other hand, it is equally possible that the defect in hypertension lies primarily in the binding of vasoactive substances or in the metabolism of smooth muscle contraction. This defect would appear no matter what vasoactive substance was used to stimulate the muscle.

It has recently been observed that reactivity to infused l-norepinephrine is not

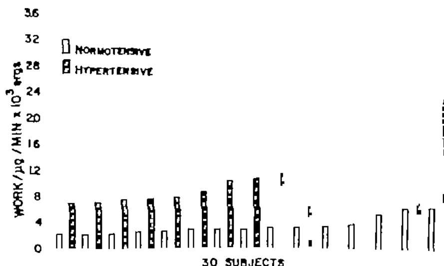


Fig. 1. Work of vasoconstriction per microgram of angiotensin (AT) infused per minute in 30 subjects.

only affected by the amount of l norepinephrine stored in the tissues[19] but also by glucocorticosteroids[3] and by sodium depletion.[4] It is likely therefore that the activity of the chemical system involved is not only determined by hereditary transmission itself but also by activators co factors and inhibitors some of which could be influenced by acquired disease

Summary

1 Digital vascular reactivity to infused angiotensin II was measured in 15 normotensive subjects and 15 patients with essential hypertension

2 This reactivity was found to be increased in the hypertensive group

3 The mechanisms involved are discussed

We are grateful to Dr W E Wagner of Ciba Company for supplies of angiotensin II and to Dr I C Winter of G D Searle and Company for supplies of SC 1950

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The effects of amyl nitrite and phenylephrine on the intracardiac murmurs of small ventricular septal defects

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The effect of amyl nitrite and phenyl ephrine on the externally recorded murmurs of ventricular septal defects has been reported elsewhere from this clinic By decreasing the systemic blood pressure amyl nitrite produces a brisk drop in left to right ventricular gradient with resultant reduction in left to right shunt across the defect and an easily *appreciated softening and shorten* ing of the regurgitant systolic murmur Phenylephrine on the other hand elevates the systemic blood pressure causing a sharp rise in left to right ventricular gradient with resultant increase in left to right shunt across the defect and an easily detected intensification and prolongation of the murmur

Ejection murmurs aortic and pulmonary on the other hand are strikingly intensified after amyl nitrite as a result of the increased cardiac output and velocity of ejection Phenylephrine however has a variable effect or no effect on these murmurs

In the case of small ventricular septal defects (less than 45 per cent left to-right shunt and normal hemodynamics) it is generally accepted that the pansystolic murmur is produced at the site of the defect in the ventricular septum Though the loudness of the murmur bears little relation to the size of the defect small defects are usually associated with particularly *loud murmurs which radiate fairly widely* Consequently associated pulmonary ejection murmurs may often be incorporated in the externally recorded murmur of ventricular septal defect Since ejection and regurgitant murmurs behave differently after amyl nitrite and phenylephrine the behavior of the external murmur may not truly represent the behavior of the individual murmurs within the heart It was thought desirable therefore to investigate the effects of these vasoactive drugs on intracardiac murmurs since it has been shown that the phonocatheter can selectively record murmurs at their site of production By using

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simultaneously recorded internal and external sound tracings, we could determine how closely the murmur at the chest wall represented the murmurs within the heart. The uncomplicated situation of small ventricular septal defect without pulmonary stenosis was chosen for this study.

It has only recently been appreciated that the murmur of small ventricular septal defects need not be pansystolic.[5] Elsewhere[6] we have shown that a short early systolic murmur is characteristic of minute ventricular septal defects. The clinical and phonocardiographic features of this defect were defined and the methods whereby the diagnosis could be established described. In this paper further observations on the intracardiac murmurs of minute ventricular septal defects will be reported.

Material and methods

Two groups of patients were investigated. (A) Eight patients with *small ventricular septal* defects comprised one group (Table I). The right ventricular and pulmonary arterial pressures were normal and there was no gradient between the main pulmonary artery and the high right ventricle. In 7 the shunt was localized to the ventricle by saturation data (range 14 to 44 per cent). (B) Four patients with *minute ventricular septal* defects were similarly studied (Table I). The shunts were so small that they could not be detected by routine cardiac catheterization methods and systemic arterial dye dilution techniques. However, the technique of employing two venous catheters for obtaining dye dilution curves from the right heart successfully established the diagnosis.[6,7]

Sound tracings were obtained with the phonocatheter in the right atrium, right ventricle, and pulmonary arteries and recorded synchronously with a sound tracing from the chest wall at the site of maximal intensity of the murmur, usually the fourth left intercostal space. High frequency recordings were made at fast paper speed (75 to 80 mm./sec.) by means of the V.E.P. multichannel recorder for both intracardiac and extracardiac sound tracings.

The barium titanate piezoelectric crystal phonocatheter and preamplifier was used* for intracardiac sound recordings. The amplification used on both was purely qualitative, but once selected remained unchanged throughout the administration of amyl nitrite and phenylephrine. No attempt was or could be made to measure or compare the frequency and intensity of murmur generated within the heart and that on the chest wall. Positioning of the phonocatheter in the right ventricle was sometimes extremely critical and it was not always easy to keep the tip of the catheter in the same position from cycle to cycle. Small shifts in the position of the tip could result in changes in duration, shape, and amplitude of the murmur. This was particularly important in the case of minute ventricular septal defects wherein the jet murmur may be very much localized and in an unusual position.

When the phonocatheter was positioned at the optimal site (by means of oscilloscopic control) within the right ventricle, the effect of amyl nitrite and phenylephrine on synchronously recorded external and internal murmurs was studied by means of methods previously described. After phenylephrine the patient was usually unaware of side effects, remaining relaxed and quiet throughout. With amyl nitrite, however, the procedure involved several rapid deep respirations and produced uncomfortable subjective sensations and tachycardia. This gave rise to difficulty in keeping the tip of the phonocatheter in the same position in the inflow tract of the right ventricle, so that whenever possible the tip was kept in the outflow tract where its position was less apt to shift. If at the end of the test the murmur had not returned to the control intensity and configuration, it was assumed that the tip had moved and the test was repeated.

Results

A. Small ventricular septal defects. The results are shown in Table I. In some patients intrapulmonary arterial phonocardiograms showed an ejection murmur which differed completely from the murmur recorded in the right ventricle and from that of the phonocardiogram from the chest wall. In 3 subjects the pansystolic murmur in the right ventricle radiated widely through the whole pulmonary arte

*Supplied by the American Electronics Laboratory.

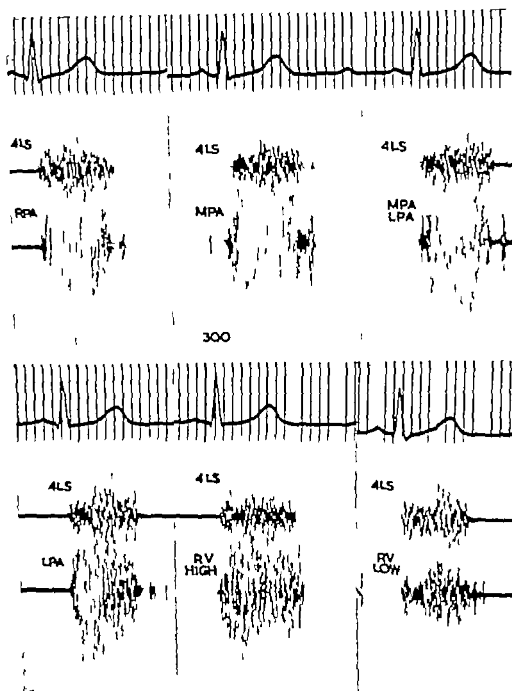


Fig. 1 Synchronous external phonocardiogram at the fourth left interco tal space (*4LS*) and internal phonocardiogram in the pulmonary arteries and right entricle in pati t with small entricular septal defect (Case 3 A P) All phonocatheter tracings ere taken at the same t tenuation *300* The plateau type of pansystolic murmur with light end systolic crescendo well show The murmur is far louder in the pulmonary arteries than in the right entricle In the high right ventricle the murmur is longer going beyond the aortic second sound which obscured although the murmur is not so intense as in the pulmonary arteries I the low right entricl the murmur is softer but remains pansystolic The jet from the entricular septal defect is presumably transmitted directly into the pulmonary arteries and not into the rest of the right entricular ca ity

Table I

Case	% L R shunt	PAP (mm Hg)	Infund bular gradient (mm Hg)	External PCG
		Small Ventricular Septal Defect		
1 I O	44	23/10	6	I nsystolic l te systolic crescendo at PA and 4LS Splitting 0 01 sec
2 J B	14	25/13	0	I ansystolic plateau with slight end systolic cre c ndo at PA and 4LS Splitting 0 02 sec
3 A P	24	22/ 9	0	I ansystolic plate u h ped t PA nd 4LS Splitting 0 04 se
4 L K	43	24/10	0	I s tolic l t cre endo t P A nd 4LS Splitt ng 0 04 se
5 I R	30	20/ 8	12	I ns t lic l t crescendo t P A nd 4LS Spl tting 0 04 sec
6 H V	24	17/ 8	0	I nsystolic pl t u sh ped t P A and 4LS Spl tting 0 04 sec
7 I M	25	35/10	0	I nsystolic l te systolic crescendo t P A nd 4LS Splitting 0 06 sec (RBBB)
8 G C	25	24/12	0	I nsystolic pl t u t P A nd 4LS Spl tt ng <0 02 sec
		Minute Ventricular Septal Defect		
1 L T	7	20/10	0	Short early crescendo t PA nd 4LS I ject n SM t PA Spl tting 0 02 sec
2 F K	3	25/13	0	Short early crescendo t PA and 4LS Splitting 0 02 sec
3 T A	7	14/ 5	0	Short early crescendo
4 M V	Minut	21/11	0	Short early crescendo t PA an l 4LS

PAP Pulmonary arterial press re PCG Phonocardi gram PA Pulm nary artery 4LS F rth l ft I costal space

Pulmonary artery PCG	Right ventricular PCG	Amyl nitrite	Phenylephrine
Small Ventricular Septal Defect			
Short ejection midsystolic crescendo	Pansystolic all sites mid systolic crescendo	Softens	—
Pansystolic	Pansystolic all sites plateau-shaped	Softens shortens	Intensifies prolonged
Pansystolic plateau very loud	Pansystolic all sites plateau high mid systolic crescendo low	Softens	Intensifies prolonged
Short ejection mid systolic crescendo	Pansystolic all sites mid systolic crescendo	Softens	Intensifies
Short ejection mid systolic crescendo	Pansystolic all sites but in intensity rises early crescendo	Softens	Intensifies
Nil	Pansystolic all sites mid systolic crescendo	Softens	Intensifies
Nil	Pansystolic all sites [illegible] systolic crescendo	Softens	Intensifies
Pansystolic plateau	Pansystolic all sites plateau shaped maximal at apex	Softens	Intensifies prolonged
Muscular Ventricular Septal Defect			
Short mid systolic ejection murmur	Short early crescendo local mid at apex	—	—
Ejection SM and pan systolic louder than in RV	Early crescendo but pan systolic	Softens shortens	Intensifies
Ejection SM and mid systolic crescendo	Short early crescendo localized low right ventricle	Softens shortens	Intensifies prolonged
Mid systolic ejection SM and systolic crescendo	—	—	—

SM [illegible]

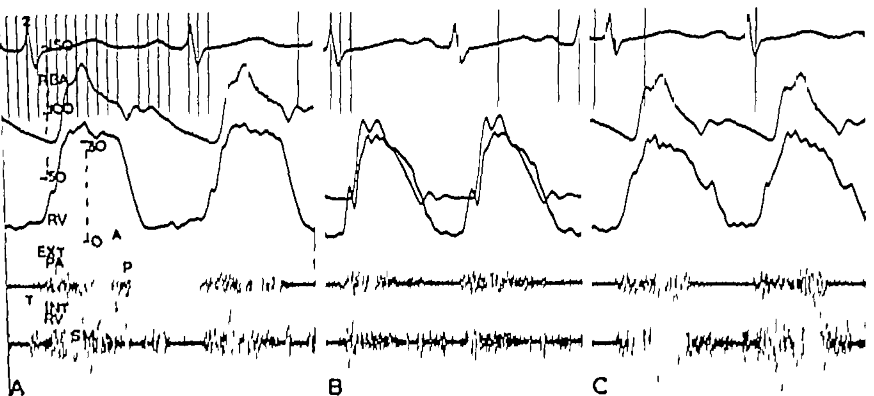


Fig. 2. [illegible] (B) the murmur [illegible] (C) [illegible] amyl nitrite [illegible] by 15 [illegible] mm. Hg.

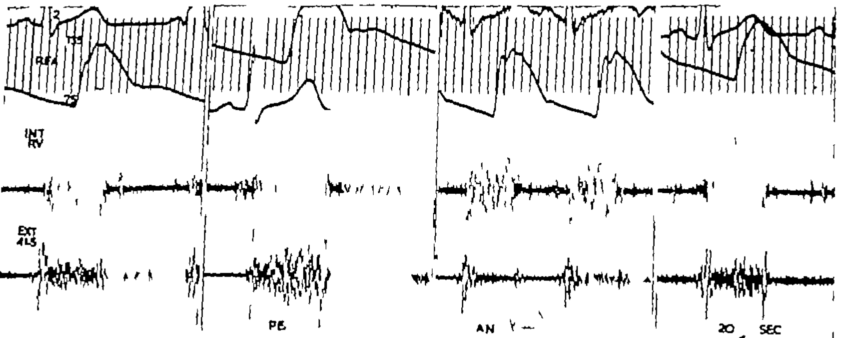


Fig. 3 Tracing from a patient with small ventricular septal defect (Case 2, J.B.) showing the effect of phenylephrine followed by inhalation of amyl nitrite on the synchronously recorded external murmur (*4LS*) and the murmur recorded in the right ventricle (*INT RV*). The plateau-shaped systolic murmur is greatly intensified and prolonged at both sites after phenylephrine (*PE*) which elevated the systemic blood pressure from 137/72 to over 1 5/113 mm Hg. Amyl nitrite given at the height of the phenylephrine effect produced striking softening of both murmurs when the systemic pressure fell to 1 5/63 mm Hg. Twenty seconds later when the effect of amyl nitrite had worn off the blood pressure rose to 150/98 mm Hg with striking reintensification of the murmurs.

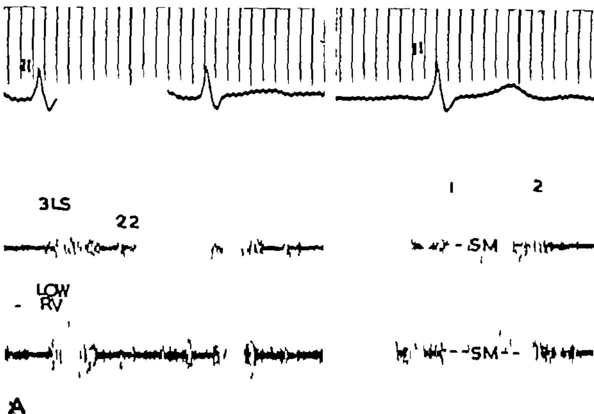


Fig. 4A. Effect of phenylephrine on the simultaneously recorded external and intra-right-ventricular sound tracings in Case 3 (T. A.) with minute ventricular septal defect. Before phenylephrine short early high-frequency crescendo-decrescendo murmurs of identical pattern are recorded from both sites. After phenylephrine both murmurs intensify and lengthen considerably; the murmur now becomes pansystolic although preserving a diamond-shaped configuration. Note the bradycardia (55/min.) and closing of the split second sound after phenylephrine. The multiple noise artifacts in the phonocatheter channel are probably due to friction against the second catheter in the pulmonary artery.

nal system (Fig. 1) so that if a murmur due to pulmonary flow was present it was engulfed by the murmur due to ventricular septal defect. In every case phonocardiograms from the right ventricle showed high-frequency pansystolic murmurs but the site of maximal intensity varied.

The effect of amyl nitrite on the synchronously recorded intraventricular and external murmurs was studied in 8 patients. In each patient both murmurs softened and recovered in parallel fashion (Figs. 2 and 3). Administration of amyl nitrite was repeated in one patient with the phonocatheter in the pulmonary artery. The intrapulmonary murmur was purely an ejection systolic murmur totally dissimilar to the loud pansystolic intraventricular murmur. The intrapulmonary ejection murmur became louder but the murmur recorded on the chest wall at the pulmonary area softened.

Phenylephrine was administered in 7 patients with the phonocatheter in the right ventricle. Marked intensification and prolongation of the murmur was recorded externally and internally; the changes in both murmurs again followed each other in closely parallel fashion, although the intensification of the intracardiac murmur was often more explosive (Fig. 3). In 3 patients amyl nitrite was administered during the peak action of phenylephrine. Both murmurs promptly softened during the fall in blood pressure, but with the return of phenylephrine action the murmurs quickly intensified (Fig. 3). In one patient phenylephrine was administered when the phonocatheter was in the pulmonary artery. The ejection systolic murmur intensified but did not become pansystolic.

B. Minute ventricular septal defects. The results are shown in Table I. An ejection

systolic murmur which was recorded within the main pulmonary artery in 3 patients differed from both the intraventricular and the chest wall murmur. In one patient, however, the intrapulmonary murmur was pansystolic and resembled both the murmur on the external phonocardiogram from the pulmonary area and the murmur recorded in the right ventricle. The murmur was louder in the pulmonary arteries than in the right ventricle (Table I).

Phonocardiograms from the right ventricle were obtained in 3 patients. In one a soft, short, high frequency murmur with early crescendo and decrescendo could only be recorded at the apex of the right ventricle. In the other 2 patients high frequency murmurs were recorded in the outflow tract of the right ventricle. In one the murmur had an early crescendo but was pansystolic, and in the other the murmur was short with a striking crescendo decrescendo in early systole (Fig. 4).

Amyl nitrite was administered to 2 patients with the phonocatheter in the right ventricle and the external phonocardiogram was recorded in the fourth left intercostal space. At both sites there was prompt softening of the murmur (Fig. 4A). In one subject the intrapulmonary ejection systolic murmur intensified but the chest wall murmur softened. Presumably the intrapulmonary murmur failed to reach the chest wall even when intensified and the chest wall murmur represented the atypical regurgitant murmur of minute septal defect. In another subject the murmur recorded at the fourth intercostal space had the characteristic features described for the murmur of a minute ventricular septal defect, being of high frequency and short, starting with the first sound, with an early crescendo. However, at the pulmonary area the murmur was ejection in type, associated with pulmonary flow. After the patient had inhaled

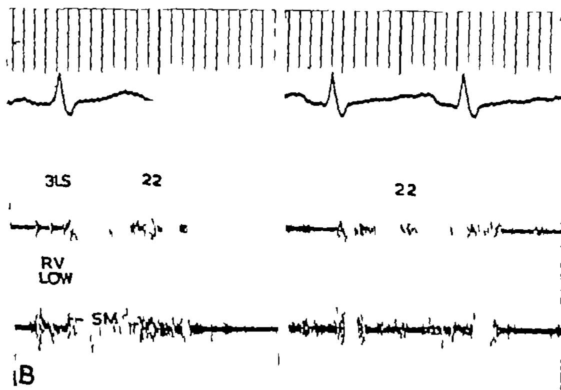


Fig. 4B. F[illegible] minutes after phenylephrine the external and internal murmurs are still intensified but the effect of the drug is wearing off as shown by the faster pulse rate (8?/min.) and widening of the split second sound. Fifteen seconds after amyl nitrite both murmurs become strikingly softened and shortened. The response to phenylephrine and amyl nitrite proves that the intraventricular murmur is produced by the ventricular septal defect.

amyl nitrite the murmur at the fourth left intercostal space softened whereas the murmur in the pulmonary area intensified

Phenylephrine produced marked intensification of both the *intra right ventricular and the chest wall murmurs in 2 patients* studied (Fig 4A) The murmur lengthened and became clearly pansystolic thus being identified as a murmur due to ventricular septal defect In another patient the *intrapulmonary* systolic murmur softened while the chest wall murmur intensified

Discussion

Small ventricular septal defects in the absence of pulmonary stenosis or pulmonary hypertension are characterized by the presence of a loud pansystolic murmur maximal at the fourth left intercostal space often associated with a thrill The murmur is usually plateau shaped or has a late crescendo Splitting of the second sound may be normal but often is found to be surprisingly wide on phonocardiography The width of splitting however is not appreciated clinically because of the length and loudness of the systolic murmur When the crescendo is late in systole the *murmur* drowns *the* aortic *sound* and frequently spills over beyond it The murmur of a ventricular septal defect in fact is so loud that it dominates the auscultatory findings and obscures any other systolic murmur that may also be associated

This study shows that the murmur recorded from the chest wall by the crystal microphone strikingly resembles the murmur recorded in the right ventricle by the barium titanate phonocatheter This murmur is presumably produced at the site of the defect and may radiate down the pulmonary arteries or stop at the pulmonary valve When the murmur due to the septal defect is not transmitted into the pulmonary arteries a separate intrapulmonary ejection systolic murmur is recorded At the chest wall however two separate murmurs are not detectable because of wide radiation of the loud septal-defect murmur

Amyl nitrite produces a drop in peripheral resistance a reduction *in left ventricular* pressure a fall in gradient between the left and right ventricles and a reduction in left to right shunt This softens the murmur produced at the site of the defect in the ventricular septum as confirmed by the phonocatheter With the increase in cardiac output however there is increased velocity of flow across the pulmonary valve causing slight intensification of the pulmonary ejection murmur shown by the phonocatheter Since the noise produced at the ventricular septal defect dominates the auscultatory findings the over all effect is softening of the murmur

Phenylephrine has an effect opposite to that of amyl nitrite by increasing systemic resistance increasing interventricular gradient and increasing the left to right shunt and thus intensifies the murmur produced at the site of the defect in the ventricular septum as has been shown with the phonocatheter However because the cardiac output is reduced with little alteration in stroke volume the effect on the pulmonary ejection murmur is negligible

It may thus be concluded that in the case of uncomplicated small ventricular septal defect the chest wall murmur accurately represents the intraventricular murmur and therefore should provide a rough quantitative index of the volume rate of shunt flow Thus intensification of murmur indicates increased volume rate of shunt flow and vice versa

In the case of larger defects and in the presence of pulmonary stenosis the interplay of murmurs must be borne in mind when interpretation of the effects of amyl nitrite is made Chest wall murmurs represent a fusion of loud ejection and regurgitant murmurs and amyl nitrite intensifies the former and diminishes the latter Although regurgitant flow may be considerably diminished after amyl nitrite the softened regurgitant murmur is counterbalanced by intensification of the ejection murmur resulting in atypical behavior of the external murmur[1] Intracardiac phonocardiography may throw further light on this problem

Unlike the murmur due to small ventricular septal defect the murmur produced by a minute ventricular septal defect is much softer and more localized Characteristically it commences immediately with the first sound reaches a crescendo by the first third of systole and then softens

rapidly, apparently ceasing well before the aortic second sound.[6] Intracardiac phonocardiography is a useful aid in diagnosis. The murmur is recorded in the ventricle and may be critically localized. It has the same configuration as that of the external murmur. It softens after amyl nitrite and intensifies after phenylephrine, becoming pansystolic. However, in the pulmonary artery the soft ejection systolic murmur intensifies after amyl nitrite and changes insignificantly after phenylephrine. Unlike the murmur due to small ventricular septal defect, the murmur of minute defect is softer and more localized, so that it will not obscure an associated pulmonary ejection murmur if audible externally. Since the atypical murmur of septal defect is short (and early) and may closely resemble an associated pulmonary ejection murmur, great care must be taken to select the correct site for auscultation during the amyl nitrite test. Moreover, because the ejection murmur will intensify after amyl nitrite, the diagnosis will be missed unless the site of maximal intensity of the septal defect murmur is selected.

The intracardiac murmurs both of small and of minute ventricular septal defects differed in their position and direction of conduction, suggesting different sites of the defects or direction of the regurgitant jet within the ventricle. It was not possible, however, to determine whether the defect was in the muscular or membranous septum or whether the defects were single or multiple. This was due in part to difficulty in accurately identifying the position of the tip of the catheter within the right ventricle during fluoroscopy in the anteroposterior view. In only one patient was there strong evidence of a minute septal defect low down in the muscular septum. In this patient the only murmur recorded within the right ventricle was confined to the apex of this chamber.

Summary

1. Synchronous external and internal phonocardiographic tracings were recorded in 8 patients who had small ventricular septal defect (less than 45 per cent left-to-right shunt) and normal pulmonary arterial pressure and were without pulmonary stenosis. The external phonocardiograms showed a widely radiating pansystolic murmur, either plateau shaped or with a late crescendo. The internal phonocardiogram showed a similar murmur in the right ventricle. In 3 patients the murmur due to the ventricular septal defect radiated widely into both pulmonary arteries but was not equally loud at all sites in the right ventricle, suggesting jet flow of shunted blood down the pulmonary arteries. In 3 patients the septal defect murmur was confined to the ventricle and a separate pulmonary ejection murmur was recorded beyond the pulmonary valve.

2. Amyl nitrite softened the pansystolic regurgitant murmur recorded in the right ventricle. In the pulmonary artery, however, the short ejection murmur was intensified, but this had no influence on the externally recorded murmur, which also softened.

3. Phenylephrine produced marked intensification and prolongation of the murmur in the right ventricle and of the externally recorded murmur, and in one subject the intrapulmonary ejection murmur intensified.

4. Since changes in the chest wall murmur closely parallel changes in the right ventricular murmur, variation in intensity of the chest wall murmur alone provides information of the change in volume rate of shunt flow.

5. In the case of minute ventricular septal defect the tracings recorded at the fourth left intercostal space and in the right ventricle both showed the characteristic crescendo-decrescendo murmur which softened after amyl nitrite and intensified and lengthened after phenylephrine. The intrapulmonary ejection murmur increased with amyl nitrite. Since the septal-defect murmur is softer and more localized in the case of minute septal defect, a separate pulmonary ejection murmur may be heard in the pulmonary area. Unless auscultation is made at the correct site, the diagnostic effect of amyl nitrite may not be detected.

6. This study has thrown some light on the different behavior of the regurgitant systolic murmur of ventricular septal defect and the pulmonary ejection murmur under the influence of vasoactive drugs. It has clarified the interpretation of these murmurs when they are heard at the chest.

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The vectorcardiogram in normal young adults
Frank lead system

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Coincident with rapid advances in the therapy of heart disease a need for more accurate diagnosis has been recognized. The application of vectorial principles in electrocardiography and later of vectorcardiography itself has been a diagnostic aid of as yet undetermined extent. Since the most recent advances in cardiology have occurred in the fields of congenital and rheumatic heart disease, need for information about normal ranges in a comparable age group is apparent. It is the purpose of this paper to supply vectorcardiographic data in normal young adults, a group in which the existence of severe arteriosclerotic changes can be fairly well excluded and yet in which the normal evolutionary changes in electrical axis from childhood to adulthood will already have occurred.

Methods and material

Sixty subjects without a history of heart disease were selected on the basis of normal findings by physical examination, electrocardiogram, and chest x-ray examination. The ages ranged from 18 to 36 years (Table I). Most of the subjects were residents, fellows, or student nurses at the Peter Bent Brigham Hospital.

The technique of vectorcardiographic registration was that devised by Frank, using the fifth intercostal space. Scalar vectorcardiographic leads were not recorded. The recording apparatus consisted of two Tektronix preamplifiers and a DuMont oscilloscope mounted on a portable unit. Vectorcardiographic loops were recorded on XXX Kodak 35 mm. film. After processing, the films were read on a Documat Microfilm Reader (Model F). In all subjects an electrocardiogram was recorded with a Sanborn direct writing electrocardiograph. This included the 12 standard leads and Leads V_{3R} and V_{4R}. The tracings were taken on the same day as the vectorcardiogram.

The vectorcardiographic loops were interrupted 400 times per second so that consecutive dashes are represented by 0.0025 second, and four dashes and their

Table I. Patient distribution

Age group (years)	Male	Female	Total
18–30	1	34	55
31–36	4	1	5

From the Medical Clinic, Peter Bent Brigham Hospital, and Department of Medicine, Harvard Medical School, Boston, Mass.
This investigation was carried out during the tenure of Postdoctoral Fellowships (HF-4390, Dr. Forkner, and [illegible] Dr. Hugenholtz) [illegible] National Heart Institute, United States Public Health Service, and was supported in part by [illegible] Peter Bent Brigham Hospital.
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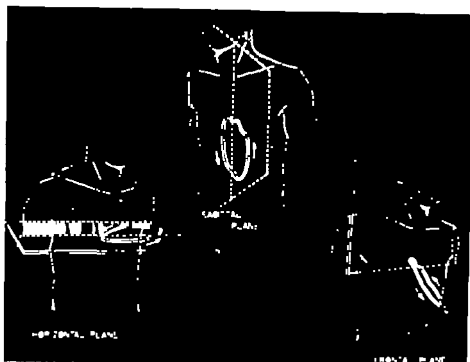


Fig. 1. Schema designating position of the three mutually perpendicular planes in the human torso.

intervals indicate 0.01 second. The teardrop-shaped dashes point in the direction of rotation. The sagittal plane was viewed from the patient's left shoulder, so that a counterclockwise rotation of this loop was observed (Fig. 1).

The direction of instantaneous 0.01, 0.02, 0.03, and 0.04 second QRS (QRSsÊ) vectors as well as maximum QRS vectors were carefully measured in each plane and plotted on a polar coordinate scale, using the notation proposed by Helm (Fig. 2). In addition, maximum P and T loop vectors were computed and their directions of rotation noted. Maximal QRS, P, and T vectors are those of largest magnitude in each planar projection. Analysis of P, T, and initial QRS vectors was facilitated by the use of augmented spot films of these areas. Vector magnitude was not measured. Terminal vectors were not calculated.

Results

A representative vectorcardiographic tracing is shown for purposes of orientation (Fig. 3). A statistical analysis of P, QRS, and T loops is listed in Table II and presented graphically in Figs. 4 through 8.

The range for the direction of maximal

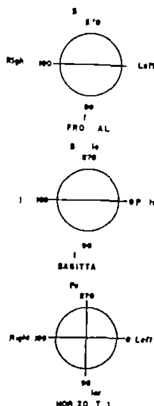


Fig. 2. System of rotation used throughout study (Reference 2). Sagittal plane viewed from left shoulder.

QRS vectors in the frontal plane was 5 to 60 degrees with a mean value of 40 degrees (Fig 5) This range was considerably narrowed when the determinations were subdivided according to the direction of rotation of the frontal plane QRS loop Thirty two showed clockwise (CW) rotation and a mean axis of 41 degrees (S D 10 1 degrees) 10 demonstrated counterclockwise (CCW) rotation and a mean axis of 20 degrees (S D 13 6 degrees) and 18 were found to have a figure-of-eight configuration and a mean axis of 42 degrees (S D 8 9 degrees) The range for this value in the sagittal plane was 335 degrees through the zero line to 118 degrees with the main distribution between 50 and 104 degrees (mean 65 degrees) (Fig 6) In the horizontal plane maximum QRS vectors were also distributed in two general groups the smaller group of only 4 observations had a mean QRS at 257 degrees and the larger group (56 observations) had a range of 320 to 27 degrees with a mean vector of 346 degrees (Fig 7) These groups did not differ significantly with regard to age or physique

The direction of the 0 01 second QRS vector in the frontal plane showed extreme variations covering the entire angular scale (Fig 5) This might be attributed at least in part to the difficulty of isolating the zero point However this explanation seems unlikely for the following reasons No such wide ranges were found for the direction of the 0 01 second vector in the sagittal and horizontal planes This does not exclude errors in measurement in the frontal plane Such errors might be of the following nature failure of proper identification of the dash structure representing the 10 millisecond time instant and error in measurement of the direction of this vector because of its small magnitude It was found that the chance of error could be reduced by careful photog

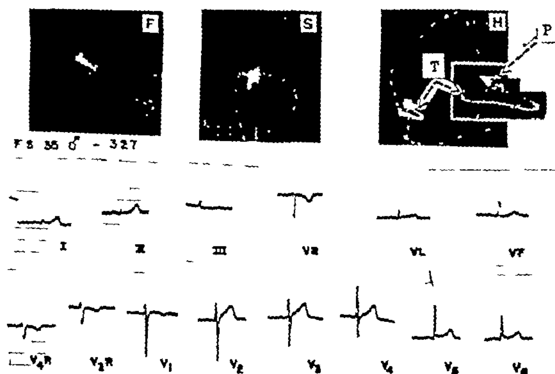


Fig 3 Representative normal vectorcardiogram in 35 year-old healthy man F Frontal plane S Sagittal plane H Horizontal plane Direction of rotation indicated by the sharp end of the tear shaped dots which interrupt the vectorcardiogram at 0 0025 second interval Frontal plane clockwise sagittal plane counterclockwise horizontal plane counterclockwise The horizontal plane insert shows the P loop (P) and the T loop (T) amplified (arrows) Amplification in the horizontal plane is greater than that in the frontal and sagittal planes

Table II Mean values of selected initial vectors in 60 healthy young adults

	Frontal plane				Sagittal plane				Horizontal plane			
	Mean	S D	S E	Number of determinations	Mean	S D	S E	Number of determinations	Mean	S D	S E	Number of determinations
QRS vectors (seconds)												
0 01	346	Wide scatter	—	60	187	25 5	3 3	60	98	25 6	3 3	60
0 0	33	22 4	9	60	151	25 1	3 3	60	50	24 2	3 1	60
0 03	39	10 6	1 4	59	107	29 5	3 8	60	8	15 6	2 0	60
0 04	68	61 8	8 0	59	63	24 8	3 2	59	343	25 0	3 3	60
Maximum	40	10 6	1 4	60	65	31 2	4 1	60	346 257	30 5 —	4 0 —	56 4
Maximum QRS vector arranged according to direction of rotation	41 (Range 20 60)	10 1	1 8	32CW	—	—	—	—	—	—	—	—
	70 (Range 5 90)	15 6	4 3	10CCW	65	31 2	4 1	60CCW	346 257	30 5 —	4 0 —	56CCW 4CCW
	4 (Range 13 55)	8 9	2 1	18 Figure-of eight	—	—	—	—	—	—	—	—
Maximum P vectors	64	19 9	2 8	49	98	11 0	1 5	5	356	19 4	2 7	51
Maximum T vectors	40	17 7	2 6	48	104	27 3	4 1	43	16	24 7	3 6	48

*Of the 59 determinations, 1 were found in counterclockwise (CCW) loops, mean al 90 S D 10° S E 3 1 17 in figure-of-eight loops at 41 S D 14 8 S E 4 1 the mean 24 of the 32 of clockwise (CW) loops the mean value 44 S D 14.2 th S E 3 1 The remainder with CW tion showed de nd (see Fig 3)

raphy of greatly amplified early segments of the loop Duplicate measurements indicated an average error of 5 degrees The correctness of these measurements appears to be further supported by the small standard deviation found for the 0.02 and 0.03 second vectors because if an incorrect zero point had been selected the error would have propagated itself throughout all subsequent observations

Since there was no distinct correlation of this early vector with the direction of rotation of the QRS loop in the frontal plane it seemed most likely that this variability (also found by Pipberger[1]) was related to the degree of superior deflection

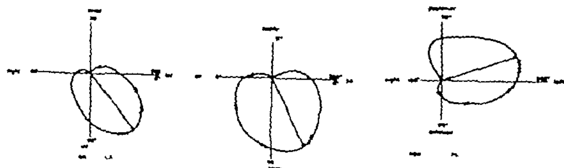


Fig 4 Representative normal QRS loop in three planes derived from 60 normal adults In this and succeeding figures the arrows indicate direction of rotation and location of instantaneous vectors in accordance with the following scheme → average vector at 0.01 second →→ average vector at 0.02 second →→→ average vector at 0.03 second →→→→ average vector at 0.04 second The line connecting the zero point with the most distant point of the loop represents the maximum QRS vector

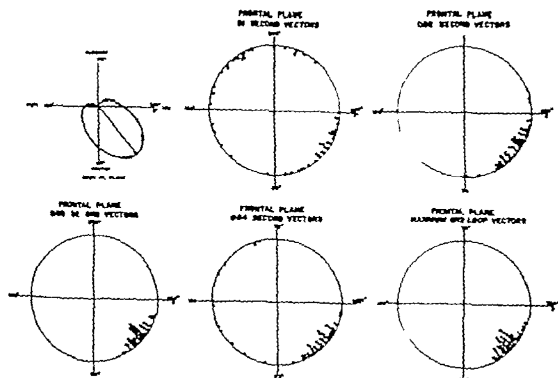


Fig 5 Scattergrams indicating position of the 0.01 0.02 0.03 0.04 second and maximum QRS vectors of 60 healthy adults in the frontal plane There is wide divergence in the 0.01 second vectors but a narrow range for the other vectors. The standard deviation and standard error of the mean for each vector are given in Table II

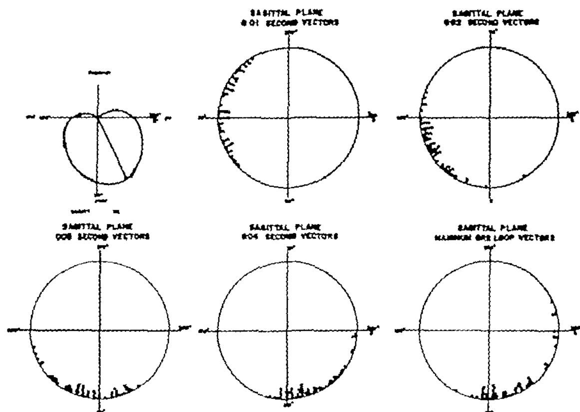


Fig. 6. Scattergram indicating position of the 0.01, 0.02, 0.03, 0.04 second, and maximum QRS vectors of 60 healthy adults in the sagittal plane.

of the ventricular activation curve as the impulse spread from the proximal branches of the bundle of His. Directions of initial vectors for the sagittal and horizontal planes are given in Figs. 6 and 7. As projected on these planes, the 0.01 second vectors pointed mainly anterior and rightward and were distributed over a comparatively narrow range (S.D. respectively 28.5 and 25.6 degrees). The differences between the directions of various vectors calculated in each plane were statistically significant ($p < 0.001$) with the exception of the 0.02 and 0.03 second vectors in the frontal plane.

In each of the three planes the respective observations for the 0.02 and 0.03 second vectors were located close together (see Figs. 5, 6, and 7), resulting in relatively small standard deviations. This also was observed with the 0.04 second vector in the sagittal and horizontal planes. In the frontal plane, however, the 0.04 second vectors were widely distributed, the standard deviation of 61.8 degrees contrasting sharply with that of 25.0 degrees for the 0.04 second vector in the horizontal plane. It appears that this wide spread is a function of the direction of rotation of the loop. Since the maximum QRS vector in the frontal plane is closer to the 0.03 second vector than to the 0.04 second vector, the 0.04 second vector of those normal subjects with counterclockwise rotation was found to be on the leftward ascending limb of the QRS loop, whereas in the normal subjects with clockwise rotation it was situated on the rightward ascending limb (Fig. 5). When the values of the 0.04 second vector were subdivided according to direction of rotation, much smaller standard deviations were found. Obviously, the mean value of 68 degrees for the 0.04 second vector has only limited significance since it represents principally the larger number of normal subjects with clockwise rotation. The more logical subdivision of the 0.04 second vector in the frontal plane according to direction of rotation is given in Table II.

Of the 60 determinations, the direction of rotation in the frontal plane was clock-

wise in 32 counterclockwise in 10 and figure of-eight or linear in 18 There was no individual with a maximum QRS vector of less than 20 degrees who demonstrated clockwise rotation in this plane Although there was no apparent relationship between the age of the subject and the direction of the maximum QRS vector the more horizontally located maximum QRS vectors (mean 20 degrees) were associated with counterclockwise rotation The reverse was true for the more vertically situated maximum QRS vectors (mean 41 degrees) In all subjects rotation of the QRS loop was counterclockwise in the sagittal and horizontal planes

The maximum P and T vectors are summarized in Table II and Fig 8 (*A B C*) In general the P vectors tended to fall within a narrower range and to be oriented in a more inferior rightward and posterior direction than were the T vectors although considerable overlap in individual values was evident Counterclockwise rotation was the rule for the P loop in all planes Counterclockwise rotation also occurred in the T loop in the sagittal plane in all but 7 individuals and in the horizontal plane in 57 individuals In the frontal plane the T loop rotated as frequently in a clockwise as in a counterclockwise direction

Discussion

Interpretation of electrocardiographic and uncorrected vectorcardiographic patterns derived from human beings rest on certain basic assumptions which have proved to be insufficiently accurate for recent methods of vectorcardiography These considerations have been studied by others[11] and can be summarized as follows (1) that the human body has homogeneous resistance (2) that it is a volume conductor of regular shape and (3) that the electrical center of the heart is constant and centrally located and therefore may be represented by a fixed dipole equivalent

However extensive investigation of this problem by many workers using torso models of homogeneous conductivity with different configurations of body build has shown that *effective* lead axes rarely coin

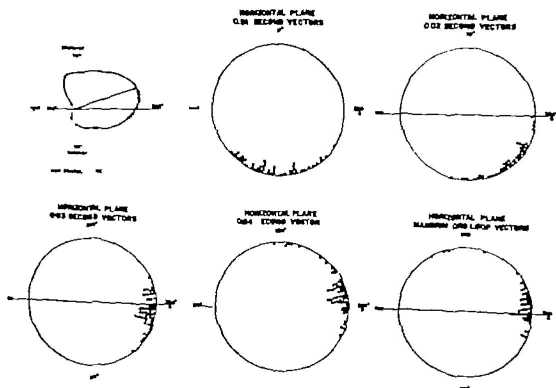


Fig 7 Scattergrams indicating position of the 0 01 0 02 0 03 0 04 second and maximum QRS vectors of 60 healthy adults in the horizontal plane

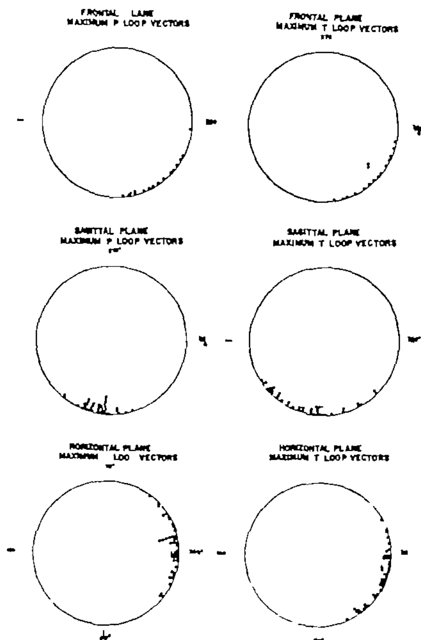


Fig. 8. Scattergrams indicating location of the maximum P and T loop vectors in the frontal plane (*A*), sagittal plane (*B*), and horizontal plane (*C*).

cide with *anatomic* lead axes either in magnitude or in direction. Nor is there any constancy of the heart dipole within the same individual.[2, 1] It has become apparent that eccentricity of heart location is the major factor and that variations in physique and tissue conductivity contribute to this discrepancy. The Frank system was devised to correct errors arising from such variables and yet to maintain clinical applicability. This study indicates that a very consistent performance yielding useful data within an acceptable range can be expected.

Comparison of the results of this analysis using the Frank system with those of Pipberger on 100 normal subjects using the SVEC III lead system[7, 11] indicates a rather close agreement for most QRS values obtained (Table III). The mean values for maximum P and T loop vectors

[illegible] Pipberger [illegible] sagittal plane has been corrected [illegible] which [illegible] of notation which views [illegible] left [illegible]

are also comparable A narrow range for the frontal plane maximum QRS vector is confirmed The same double peak contour of the maximum QRS in the horizontal plane was recorded with the present technique There are however some differences particularly in the 0 02 and 0 03 second vectors Since the 0 04 second and the maximum QRS vectors are quite comparable (frontal plane 40 versus 41 degrees sagittal plane 65 versus 55 degrees horizontal plane 346 versus 323 degrees) as are the 0 01 second vectors (sagittal plane 187 versus 201 degrees horizontal plane 98 versus 94 degrees) and the standard deviations for these vectors it does not appear that difficulties in isolating the exact beginning of the QRS loop are responsible Rather differences inherent in the design of these reference systems provide the most acceptable explanation for the observed discrepancies

In a recent study Mori and associates[11] also using Schmitt's SVEC III system analyzed initial QRS vectors in a group of older men When their measurements of elevation and azimuth are converted to the system of notation used in the present study fair agreement for the 0 01 second and 0 04 second vectors existed (Table III) Less good correspondence was found for the 0 02 and 0 03 second vector directions These findings seem again to point toward differences in the reference systems although the older age of the group studied

The m[illegible] QRS [illegible] calculated [illegible] study [illegible] good correspondence [illegible] the [illegible] QRS and th[illegible] 0 04-second vect[illegible]

*Table III Comparison with data obtained by other investigators**

Plane	Vector	Mori et al (?3 cases)	Pipberger (100 cases)	Present study (60 cases)	Bristow (7 cases)
Frontal	0 01	355 9	———	346 0	———
	S D	24 3	———	———	———
	0 0	7 7	———	33 0	———
	S D	15 6	———	22 4	———
	0 03	16 4	28 0	39 0	———
	S D	10 6	26 7	10 6	———
	0 04	2 8	38 0	30 0 /41 0 /44 0	———
	S D	13 6	1 2	10 0 /14 8 /14 2	———
	Maximum	———	41 0	40 0	33 0
	S D	———	14 9	10 6	———
Sagittal	0 01	184 1	201 0	187 0	———
	S D	24 3	28 4	25	———
	0 02	N C	179 0	151 0	———
	S D	———	21 8	23 1	———
	0 03	N C	138 0	102 0	———
	S D	———	35 6	29 5	———
	0 04	83 0	85 0	63 0	———
	S D	24 2	34 4	24 8	———
	Maximum	———	55 0	65 0 †	39 0 †
	S D	———	36 7	31 2	———
Horizontal	0 01	115 0	94 0	98 0	———
	S D	31 2	26	25 6	———
	0 02	71 1	84 0	50 0	———
	S D	31 9	23 9	24 2	———
	0 03	26 0	40 0	8 0	———
	S D	23 4	29 8	15 6	———
	0 04	338 0	356 0	343 0	———
	S D	34 2	26 4	25 0	———
	Maximum	———	323 0 †	346 0	327 0 †
	S D	———	40 6	30 5	———

*Where necessary values have been [illegible] with [illegible] system of notation [illegible] which views the sagittal pla[illegible]
[illegible] G[illegible] described

by Mori and his associates may explain some of the discrepancies This latter possibility is further indicated by the generally more horizontal direction of all initial vectors in the frontal plane when compared to Pipberger s or to our data However despite the younger age of our subjects the data obtained with the Frank system showed a more leftward and posterior direction of the initial vectors in the sagittal and horizontal planes It appears therefore that whereas good agreement exists between both systems in the frontal plane projection of spatial vectors allowing for differences in age of the subjects studied sagittal and horizontal plane projections diverge considerably The fact that the best agreement between Pipberger s and Mori s study was found in the sagittal and horizontal plane data further accents this discrepancy between the *Frank* and the SVEC III systems

Unfortunately comparable studies with the Frank system are not available Bristow showed recently however in a group of 72 mostly middle aged people that the maximum QRS vector and the half area QRS vector were displaced even farther leftward posteriorly and superiorly than in our series suggesting that increased age will further enhance the already existing tendency of the Frank system toward excessive leftward and posterior projection of spatial vectors

No comparison with the cube system was made since no detailed data or timed vectors are available Our own limited experience[15] with the latter system however suggests that as with the standard electrocardiogram a much wider range of observation exists for these selected vectors Furthermore analysis of the standard electrocardiogram does not lend itself to the description of mathematically circumscript values for individual vectors It is particularly in this regard that the vectorcardiogram obtained with a corrected lead system promises its great value

Summary and conclusions

1 The corrected vectorcardiographic lead system of Frank was applied to 60 normal young adults in order to establish preliminary normal ranges as a basis for additional studies in patients with heart disease

2 Variations observed proved to be sufficiently narrow to provide a useful basis for interpreting deviations from the norm

3 The results of this study tend to confirm those of Pipberger who used the SVEC III system in 100 normal individuals many of whom were in the same age group described in the present report

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The descending septal artery in human, porcine, equine, ovine, bovine, and canine hearts

A postmortem angiographic study

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Attention is here focused on a little known accessory artery which helps supply the cardiac interventricular septum in man and some animal species. Like the conus artery, this vessel appears to assume importance as a source of anastomotic blood supply in human hearts with diseased coronary arteries.

Materials and methods

The material consists of 427 human and 130 animal hearts. The latter include 60 porcine, 20 ovine, 15 bovine, 4 equine, and 31 canine specimens.

Each heart was studied by a modification of Schlesinger's coronary injection method: radiopaque mass of different colors was injected into the two main coronary arteries through cannulas tied securely into their respective ostia; the heart was unrolled; stereoscopic or plain angiograms of the unrolled specimens were taken; and the coronary arteries were dissected with the film as a guide. The injection mass used consists of barium sulfate in a menstruum of gelatin; it penetrates regularly to arterioles 40 to 50 micra in diameter, inconstantly to smaller arterioles, and does not enter capillaries. The source of the mass contained in any injected vessel was identifiable by its color. Stereoscopic angiograms of the intact heart were prepared in a number of cases.

The method of unrolling is that described by Rodriguez and Reiner. It lays out the main coronary arteries in one plane, leaves the interventricular septum and its blood supply intact, and transects the right coronary artery some distance beyond its origin. In the unrolled specimens and in the angiograms the proximal segment of the right coronary artery remains attached to the aorta in normal anatomic relation with the septum.

Observations

The artery with which we are concerned originates close to the right coronary orifice, descends through the superior septal border, and ramifies in the interventricular septum

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Fig 1 Coronary ngiogram of normal human heart injected by Schlesinger technique and unrolled by the method of Rodriguez and Reiner Horizontal arrow point out well-dev loped descending septal artery ertical arrow indicates the conus artery cut branches of which are ible in right lower portion of photograph Both essels arise by common ostium from the right aortic sinus close to origin of the right coronary artery Vertical lines mark the transected right coronary artery and branches and horizontal lines the left circumflex and left terior descending coronary arteries

This vessel is here referred to as the descending septal artery It is to be distinguished from the other septal arteries which arise in series from the left anterior and the right or left posterior descending coronary arteries enter the septum through the anterior and posterior septal borders and are diagonally disposed parallel to the base of the heart

The presence of the descending septal artery is inconstant It was noted in some of the human procine equine ovine and bovine hearts and was absent in all of the canine hearts studied (Table I) When present its development varied inversely with that of the superior septal branches (or branch) of the left anterior descending coronary artery When absent its distribution is taken over by the other septal vessels

Human hearts

1 Anatomy The human descending septal artery is illustrated angiographically in Figs 1 2 3 and 4 It arose from the aortic sinus in 18 hearts in 10 of these by a common mouth with the right coronary artery in 5 by an opening which also gave rise to the conus artery (Fig 1) and in 3 by a completely independent ostium (Fig 2) In 31 hearts it arose from the first centimeter of the right coronary artery main stem (Fig 3 and 4) In 2 specimens with diseased vessels we could not decide which of these types of origin was involved

From its origin the descending septal artery coursed down the root of the aorta gave off occasional branches to the peri aortic connective tissue and part of the crista supraventricularis and then entered the interventricular septum between the anterior and middle thirds of the superior septal border

The size and distribution of the descending septal artery within the septum were variable In 9 hearts this essel was poorly developed (Fig 3) Its intern l diameter

near its origin ranged from 0.3 to 0.4 mm and after a short course it broke up into tiny twigs which spread down the middle of the septum to the general level of the ramus septi fibrosi (Gross). In 11 specimens its caliber ranged from 1.0 to 1.6 mm; it extended one fourth to one half of the way down the septum, following a gentle curve which veered toward, then away from the anterior septal border (Figs. 1, 2, and 4). Its branches reinforced or replaced those of the anterior septal arteries and confronted those of the posterior septal arteries. In the other 31 hearts the descending septal artery was of intermediate size and distribution.

2. Race, sex, and age. The descending septal artery was noted in 51 hearts from 5 Negro and 46 white subjects, 35 males and 16 females (Table II). Its incidence was similar in both races, was higher in males than in females, and was unrelated to age (Table III). It is here emphasized that the incidence given refers only to vessels which were filled with mass and were visualized angiographically. A systematic search for noninjected descending septal arteries was not made.



Fig. 2. Portion of human coronary angiogram. Arrow at upper left points to independent ostium of descending septal artery close to origin of the right coronary artery. Horizontal lines indicate the left anterior and the (right) posterior descending coronary arteries which delimit the borders of the interventricular septum.



Fig. 3. Portion of angiogram of human heart with occlusions in the left circumflex and left anterior descending coronary arteries and primary branch of the latter (*lines*). Arrow points out small tortuous descending septal artery which arises from the right coronary artery and communicates with other septal arteries.

3. *Coronary pattern.*[a] The descending septal artery occurred in hearts with a right preponderant, a balanced, and a left preponderant coronary pattern.[a] No significant association between this vessel and any of these patterns was established (Table IV).

4. *Conus artery.* The descending septal artery coexisted with a conus artery in 27 hearts; in 24 it did not. Thus about 1 of every 2 hearts with a descending septal artery had a conus artery also. Our observations on the conus artery in hearts without a descending septal artery are incomplete. There is probably no relationship between the presence of one and the other of these two vessels. Schlesinger and co-workers[1] noted the conus artery in 1 of every 2 hearts that they studied.

5. *Coronary occlusions.* Coronary occlusions were present in 21 (11 males and 10 females) of the hearts with a descending septal artery. None of the occlusions involved this vessel or its origin. Most of the occlusions were old. Anastomotic filling of vessel segments distal to the occlusions was found in all of these cases.

The descending septal artery was noted twice as often in hearts with occlusions as in those without (Table V). However, its size was not demonstrably increased in the presence of occlusive disease in other cardiac vessels. Small descending septal arteries were found in hearts with occlusions (Fig. 3) and well-developed ones occurred in normal hearts (Fig. 1).

6. *Anastomoses.* Anastomoses to the descending septal artery were demonstrated in 40 hearts, of which 8 were normal, 11 had stenosing coronary atherosclerosis, and 21 had occlusions. In these 40 cases the descending septal artery must have filled with mass via anastomotic channels (at least 40 micra in diameter) because its opening was either separate from the right coronary artery (8 hearts) or proximal to the tie which secured the injection cannula into the right coronary ostium (32 hearts).

In 9 other specimens the descending septal artery arose from the right coronary artery distal to the tip of the cannula and therefore could have filled directly from its parent vessel. Information regarding the precise route of flow of the injection mass into the descending septal artery was not obtained in 2 hearts. The injection mass contained in all of the descending septal arteries visualized came exclusively from the right coronary arterial tree.

The descending septal artery lies between the left anterior and the right or left posterior descending coronary arteries and is therefore a potential route of anastomotic flow to both these major vessels of the heart. Its value as an anastomotic route is determined by its size and by the location of occlusions or narrowings in the coronary arterial tree. In 3 hearts occlusive disease involved coronary arteries in sites unrelated to the descending septal artery.

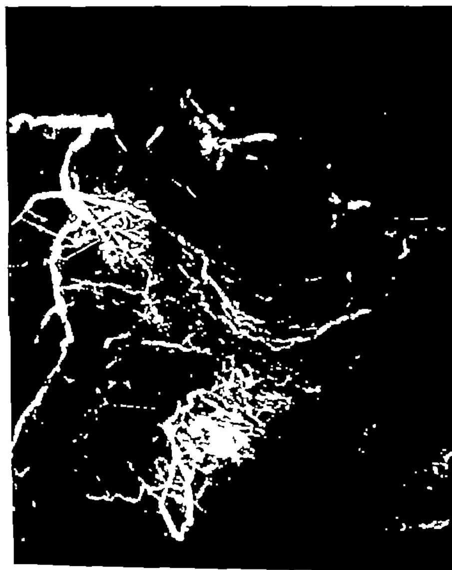


Fig. 4. Portion of angiogram of human heart with long occlusion in the middle third of the left anterior descending coronary artery and short one in the terminal end of the right coronary artery main stem (*lines*). Arrow points out well-developed descending septal artery which arises from the right coronary artery and communicates in tortuous channel with other septal arteries.

Table I Incidence of descending septal artery in human and animal hearts

Species	Descending septal artery		Total
	Observed	Not observed	
Human	51 (12%)	376	427
Bovine	15	0	15
Porcine	40	20	60
Ovine	8	12	20
Equine	1	3	4
Canine	0	31	31
Total	115	442	557

Table II Incidence of descending septal artery in males and females of the white and Negro races

Race	Sex	Descending septal artery		Total
		Observed	Not observed	
Negro	Males	4 (18%)	18	22
	Females	1 (3%)	28	29
		5 (10%)	46	51
White	Males	31 (14%)	185	216
	Females	15 (9%)	145	160
		46 (12%)	330	376
Both	Males	35 (15%)	203	238
	Females	16 (8%)	173	189
Total		51 (12%)	376	427

In 18 others this vessel was clearly in a position to help irrigate areas of the myocardium originally supplied by an occluded vessel or vessels In the angiograms of these cases anastomotic channels at least 150 micra in diameter were observed to extend from the descending septal artery to neighboring vessels These channels usually showed marked tortuosity Two of these 18 cases are illustrated in Figs 3 and 4

Animal hearts

Figs 5 6 7 and 8 show the descending septal artery in relation to the rest of the coronary arterial system in animal hearts This vessel was not observed in canine specimens its distribution in this species appears to be taken over entirely by the constant and highly developed left septal artery (Moore) (Fig 9) The resemblance between the coronary arterial patterns of man and those of these animals is evident Judged by Schlesinger s criteria [3] the bovine ovine and canine coronary patterns were all left preponderant the porcine balanced and the equine right preponderant in type

Table III Incidence of descending septal artery in various age groups

Age (yr)	Descending septal artery		Total
	Observed	Not observed	
10–19	—	2	2
20–29	—	3	3
30–39	1	10	11
40–49	1	20	21
50–59	9 (15%)	51	60
60–69	13 (14%)	78	91
70–79	18 (12%)	136	154
80–89	9 (11%)	70	79
90–99	—	6	6
Total	51 (12%)	376	427

Table IV Incidence of descending septal artery in hearts with right preponderant balanced and left preponderant types of coronary pattern[3]

Type of coronary pattern	Descending septal artery		Total
	Observed	Not observed	
Right preponderant	29 (12%)	214	243
Balanced	9 (8%)	99	108
Left preponderant	13 (17%)	63	76
Total	51 (12%)	376	4 7

Table V Incidence of descending septal artery in hearts with and without coronary occlusions elsewhere in the coronary arterial tree

Descending septal artery	Coronary occlusions		Total
	Present	Absent	
Observed	21 (41%)	30	51
Not observed	65 (17%)	311	376
Total	86 (20%)	341	427

The descending septal arteries in the animal hearts were all branches of the right coronary artery and arose close to the origin of the latter in the aorta

1 Porcine hearts The descending septal artery noted in 40 of the 60 porcine hearts was inconspicuous (Fig 5) Its diameter was 0 2 to 0 4 mm or about a third of that of the largest of the other septal arteries It descended a short way into the interventricular septum to ramify just below the superior septal border

2 Equine hearts The descending septal artery observed in 1 of the 4 equine hearts was poorly developed (Fig 6) Its diameter was 2 5 mm equal to that of a medium sized anterior septal artery in the same heart It passed down between the anterior and middle thirds of the superior septal border and continued for one eighth of the distance from the base to the apex of the septal triangle

3 Ovine hearts The descending septal artery or its equivalent was observed in 8 of the ovine hearts In 3 of these this vessel had two components each with a separate origin in the right coronary artery main stem (Fig 7) One component was short and stout and ramified close to the topmost of the posterior septal arteries Its diameter was 0 8 to 1 0 mm comparable to that of the largest of the other septal arteries The second component about half of the size of the first was long and slender It accompanied the right limb of the neuromuscular bundle all the way down the interventricular septum across the moderator band and into the right ventricular wall In 5 other ovine specimens only one of these components the short stout one was observed

4 Bovine hearts The bovine descending septal artery was highly developed (Fig 8) In each of the 15 specimens it arose from the proximal end of the right coronary artery and then passed vertically down the midline of the interventricular septum to reach the middle or inferior third of



Fig 5 Portion of coronary angiogram of unrolled porcine heart Arrow points out inconspicuous descending septal artery originating from the proximal segment of the right coronary artery main stem



Fig. 6. Coronary angiogram of unrolled equine heart. Arrows point to small descending septal artery arising from the proximal segment of the right coronary artery. Coronary pattern is right preponderant; the right coronary artery supplies the right ventricle, the posterior part of the interventricular septum, and the posterior part of the left ventricle.

this structure. Its diameter was usually 2.0 to 2.5 mm, or about half of that of the left anterior and two thirds of that of the left posterior descending coronary arteries. Its branches supplied the right limb of the *neuromuscular bundle*. It was the largest of the arteries within the septum. By comparison, other septal arteries were small indeed, the largest of these being in the order of 0.5 mm in diameter.

Discussion

The accessory vessel that we have here called the "descending septal artery" is not widely known. It was observed in 20 per cent of a series of 100 human hearts by Campbell[4] but is not described in textbooks of human anatomy,[7, 11] in many papers dealing with the coronary circulation of man,[1-3, 12] and in monographs or treatises on the subject.[19] It is depicted in the diagram of the coronary arteries published by Robb and Robb[20] and was noted in 1 of the 43 human hearts studied by James and Burch.[17] Cranmernu[14] found this vessel to be almost constant in oxen, and Bianchi[15] *noted its equivalent in the rodents Mus decumanus and Myoxus glis*. Hegazi[16] did not observe this vessel in goats, sheep, and cattle. It was probably present in the heart of an Asiatic elephant studied by Cave.[24] It is excluded from the descriptions we have come across of other elephant hearts[24, 25] and the hearts of whales,[27] horses,[1] rhesus monkeys,[27] dogs,[1, 12, 28, 29] and pigs.[29]

The conspicuous omission of this vessel in several careful descriptions of the coronary arterial system, particularly in the human being, needs to be accounted for. The ethnic difference between the populations studied by others and by us does

not seem to be a likely reason because we have observed this vessel in both Negro and white subjects. A possible explanation might be that cited by James and Burch[12] who pointed out that the interventricular septum is relatively inaccessible to anatomic examination and that techniques used for the study of its blood supply have been less than ideal. To this one might add that the presence of the descending septal artery is inconstant, that in man it is often small and easy to overlook, and that its anatomy is such that cannulas for coronary injection are probably often inserted and secured past its origin.

Campbell, who was unable to find previous mention of this vessel, proposed the name "ramus cristae supraventricularis" for it. Robb and Robb[21] label it the "superior septal artery" and note that it is "important in animals, often reduced in man (and) not mentioned by Spalteholz."

We have not adopted either of these names with reference to the first because the major area supplied by this vessel seems to be the septum itself, and with reference to the second because the same term can with justification be used to designate the topmost of the other septal arteries which arise from the left anterior and the right or left posterior descending coronary arteries.

The descending septal artery has not gained the attention that it deserves. By virtue of its position between the anterior and posterior descending coronary arteries it is a potential route of anastomotic blood flow to both. We have illustrated instances in which the descending septal artery served to bypass occlusions in neighboring large vessels. Campbell cited similar cases. It appears that the presence of the de-

For fig. 7 [illegible]

The leg[e]nd to the d[ia]gram of Robb [an]d R[o]bb[21] [la]bels th[is] vessel [an]d branches of l[e]f[t] coronary artery —appare[n]tly typographical error



Fig. 7. Coronary angiogram of unrolled ovine heart. Arrows point out two components of the descending septal artery in this species. A short stout component (*short arrow*) supplies the superior part of the septum. A long slender one (*long arrow*) accompanies the right limb of the neuromuscular bundle. Each of these components has a separate origin in the proximal segment of the right coronary artery main stem. Coronary pattern is left preponderant: the left coronary artery irrigates the left ventricle, the interventricular septum and [part] of the right ventricle; the right coronary artery supplies part of the right ventricle.



Fig 8 Coronary angiogram of unrolled bovine heart Arrow points to the highly developed descending septal artery originating from the proximal end of the right coronary artery Coronary pattern is left preponderant

scending septal artery in the human heart can favorably modify the consequences of occlusive disease involving major components of the coronary arterial tree

As an anastomotic route the descending septal artery takes on the same role in the septum that the conus artery has in the right ventricle Further comparisons between these two vessels in the human heart are of interest Data pertaining to the conus artery are those of Schlesinger Zoll and Wessler

The value of a collateral vessel is enhanced when its origin is separate from the diseased vessel system that it is to supplement The conus artery has a more favorable origin As defined it arises directly from the aorta the descending septal artery often takes off from the main stem of the right coronary artery All of the descending septal arteries in Campbell's series[4] were branches of the right coronary artery

The conus artery is the larger vessel Its diameter ranged from 0 4 to more than 2 0 mm that of the descending septal artery from 0 3 to 1 6 mm

The conus artery irrigates areas of the heart that are perhaps less essential to cardiac function than those supplied by the descending septal artery The former supplies adipose and myocardial tissue in the right ventricle whereas the latter is distributed in the septum in close proximity with important segments of the neuromuscular apparatus

Both vessels are inconstant The incidence of either is unrelated to age that of the descending septal artery is unrelated to race or coronary pattern and that of the conus artery is unrelated to sex We do not have an explanation for the different incidence of the descending septal artery in males and females of this series

The conus artery is more common It was noted in 1 of every 2 hearts the descending septal artery in 1 of every 10 This difference is probably not so great as it appears Figures quoted for the conus artery include vessels which were not filled

with mass. Those given for the descending septal artery include only injected vessels large enough to be visible with the naked eye. Campbell[4] observed the descending septal artery in 1 of every 5 hearts in his series.

Anastomotic filling of the conus artery was observed in 37 per cent of the hearts in which this vessel occurred. Comparable figures for the descending septal artery are not available. The fact that the descending septal artery was seen more often among hearts with coronary occlusions than among those without suggests increased prominence of this vessel due to an augmented, i.e., anastomotic, blood flow through it. It appears that this suggestion is not necessarily invalidated by our failure to appreciate any increase in caliber of the descending septal artery in the presence of occlusions in other cardiac vessels.

None of the descending septal arteries visualized contained occlusions. Occlusions were observed in 1.5 per cent of the conus arteries. If this difference in the incidence of occlusions between the conus and descending septal arteries is valid, it may relate to the fact that the former is largely epicardial and the latter mainly intramural in course. It is generally recognized that atheroma and its complications involve intramural vessels less often than epicardial ones. The observation that occlusions spared the proximal 1.0 cm. of the right coronary artery from which a descending septal artery arose is in keeping with that of others. Schlesinger and Zoll[13] found that almost all (96 per cent or 120 out of 125) occlusions contained in the three main coronary artery stems spared the first centimeter of the right coronary artery.

Summary

An accessory artery which helps supply the cardiac interventricular septum in man and some animal species is described. It arises from the proximal part of the right coronary artery or directly from the aorta, descends through the superior septal border, and ramifies in the septum. This vessel is here called the "descending septal artery."

It was demonstrated in 12 per cent of the 427 human, all of the 15 bovine, 40 of the 60 porcine, 8 of the 20 ovine, 1 of the 4 equine, and none of the 31 canine hearts studied by Schlesinger's technique and unrolled by the method of Rodriguez and Reiner. Its development varied within and between species.

In the *human* species it occurred in normal and diseased hearts. Its caliber ranged from 0.3 to 1.6 mm. Its incidence



Fig. [illegible] Coronary angiogram of unrolled canine heart. Descending septal artery is absent. Its expected distribution appears to be taken over entirely by the constant and highly developed "left septal artery" (Moore) in this species (arrow). Coronary pattern is left preponderant.

was unrelated to race age or coronary pattern was higher in males than in females and increased twofold in the presence of occlusions elsewhere in the coronary arterial tree The descending septal artery was found free of occlusive disease Like the conus artery this vessel appears to serve as a route for anastomotic blood flow to other vessels of the heart when these are narrowed or occluded The amount of myocardial damage resulting from coronary narrowing or occlusion may in part be determined by the presence or absence of the descending septal artery

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Q T interval and T wave amplitude after induced ventricular premature beats

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Changes in the contour, amplitude, and direction of the T wave and variations in the Q-T interval are sometimes found in the electrocardiographic complex which follows a premature ventricular beat. A relationship between these observations and arteriosclerotic or hypertensive cardiac disease has been both suggested and denied.[1-4] Levine has suggested that myocardial impairment may result in changes in the Q-T interval and T wave amplitude only after prolonged diastole after a premature beat.

The study of postextrasystolic complexes in electrocardiograms recorded during cardiac catheterization provided an opportunity for assessing the changes in Q-T intervals and T waves in patients with measured abnormality of intracardiac pressure and flow. The object of this report was to determine whether the mechanical effects of intracardiac shunts and valvular stenosis were reflected in changes in the postextrasystolic T wave amplitude and Q-T interval.

Methods and material

The electrocardiograms of 450 patients which were recorded during catheterization of the right side of the heart were examined. The age range of these patients was from 2 months to 49 years. The number of patients in each decade was as follows: 2 months to 9 years, 63; 10 to 19 years, 16; 20 to 29 years, 10; 30 years and over, 4. Either Lead I or II was recorded together with the tracing of the intracardiac pressures. Because tachycardia alone may result in changes in the T wave,[5] only 93 tracings were selected in which single or paired ventricular premature beats appeared. The diagnoses consisted of septal defects, both atrial and ventricular, tetralogy of Fallot, pulmonary stenosis, ductus arteriosus, and pseudotruncus. The patients were classified as having predominant systolic or diastolic ventricular overloading by reference to the data from cardiac catheterization concerning the presence and site of left-to-right shunts and intracardiac pressures. None of the patients was receiving digitalis.

The T wave amplitude of the complex which followed a premature beat was compared with the T wave amplitude of the normal ventricular complex which preceded the premature beat. The amplitude of each of the T waves and the duration of their respective Q-T intervals were measured. The mean values and the standard

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Table I Q T interval and T wave amplitude of complexes before and immediately after ventricular premature beat

	Q T interval (sec)		T amplitude (mm)	
	Before VPB	After VPB	Before VPB	After VPB
Diastolic over load (= 43)	0 33 ±0 05	0 33 ±0 05	2 7 ±1 3	2 8 ±1 3
Systolic over load (= 50)	0 35 ±0 07	0 35 ±0 05	3 4 ±1 7	3 3 ±1 6

VPB V ntricular premature beat

deviations for these measurements are shown in Table I The significance of the difference of the means and the difference of paired normal and postextrasystolic measurements was determined [6]

Results

There was no significant change in the mean Q T interval or T wave amplitude after the premature beat in el ctrocardio grams from patients with either systolic or diastolic ventricular overloading The differences of paired observations before and after premature beats were not signifi cant In four tracings only the amplitude of the T wave changed by 2 mm or more after a premature be it Three of these patients had lesions which resulted in sy tolic overloading and the fourth had a left to right shunt which produced a dias tolic overload

The electrocardiograms were divided into two further groups (Table II) The first group consisted of those in which the difference between the Q T interval before and that after the ventricular premature beat was equal to or greater than 0 03 second The electrocardiograms of the other patients were placed in a second group An attempt was made to assess the effect which right ventricular end diastolic pres sure might have in prolonging the Q T interval after an extrasystole The data contained in Table II show that no correla tion existed between these two measure ments Similar data were examined for patients with increased systolic pressure Prolongation of the postextrasystolic Q T interval was not related to the level of right ventricular systolic pressure

Discussion

Changes in the T wave amplitude and Q T interval after extrasystoles have been observed in the electrocardiograms of pa tients with and without cardiac disease [1-4] Mann[4] and Levine[1] reviewed several pos sible causes which have been suggested as explanations for these changes Our discussion will be restricted to a proposed hemodynamic cause All previous tudies reviewed by us were made in patients with acquired cardiac disease whereas our investigation was limited to patients with *congenital lesions with either left to right* shunts or increased intracardiac pressure We were unable to find any reports in which postextrasystolic Q T and T wave changes were assessed in relation to cardiac dynamics

Variations in the T wave and Q T in terval after a premature beat have been attributed to changes in tension and blood flow in the myocardium during the post extrasystolic pause Levine reasoned that if changes in the T wave amplitude after extrasystoles were due to the prolonged filling time then such changes should consistently accompany extrasystoles How ever he concluded from his observations that these changes were generally associated with coronary artery disease and might also occur in association with other con ditions which produced profound perman ent or transient myocardial impairment In order to explain the infrequency of T wave

Table II Difference in Q T interval before and after VPB and relationship to RV diastolic pressure

Q T difference (sec)	Total number of patients	Patients with RV diastolic pressure = or > 6 mm
0 03 or > 0 03	23	16 (69 6%)
< 0 03	70	47 (67 1%)

VPB V ntricular premature beat, RV Right

changes and alteration in Q-T interval in the absence of heart disease he suggested that there might be a latent inadequacy of blood flow to the inner layers of the myocardium and that this deficiency might be exaggerated by increased diastolic filling during prolonged postextrasystolic diastole.

This hypothesis was based in part on the demonstration by Johnston and Di Palma[7] that there was a higher pressure during ventricular systole in the inner laminae than in the more superficial layers of the myocardium. Each patient of our series had a congenital lesion which resulted in either increased diastolic filling of the ventricles from a left-to-right shunt or augmented ventricular systolic ejection pressure because of obstruction to flow. Either of these conditions might be expected to enhance the effect of any relative inadequacy of endomyocardial blood flow during prolonged postextrasystolic diastole. Results of our study did not support such a hypothesis inasmuch as the mean amplitude of the T waves did not change after an extrasystole nor was there a significant change in Q-T interval. Furthermore such variations as were observed around the mean values bore no relationship to either end-diastolic pressures or systolic pressures measured before and after the premature beat.

Summary

Single or paired premature ventricular contractions occurred in the electrocardiograms of 93 patients during cardiac catheterization. The amplitude of the T wave and the duration of the Q-T interval were measured immediately before and after the premature contraction.

There was no significant difference in the mean values for either T-wave amplitude or Q-T interval before and after ventricular premature beats.

No correlation was found between the right ventricular end-diastolic pressure or right ventricular systolic pressure, on the one hand, and individual variations of the Q-T interval and T-wave amplitude, on the other.

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Fluid electrodes for monitoring the electrocardiogram during activity and for prolonged periods of time

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Electrodes which can be used with usual leads for monitoring the electrocardiogram or used on the precordium for monitoring the electrocardiogram during rest or activity will be described. The electrodes are small, atraumatic, unencumbering, and remain attached to the skin for prolonged periods of time during strenuous activity. The electrical signal picked up by the electrode is not distorted appreciably by movement of the skin beneath the electrode nor by direct blows to the electrode. Possible applications of the electrodes will be discussed.

Materials and methods

Construction of fluid electrodes. The electrode (Fig. 1) is made by using simple laboratory materials and tools. The central well of the electrode is a 0.5-cm. segment of amber gum rubber tubing, O.D. 9/16 inch, I.D. 5/16 inch. Segments of tubing can be cut rapidly and cleanly on a band saw after the tubing is threaded on a 5/16-inch dowel. The lead wire is stranded tinned copper, A.W.G. No. 26 with light wall vinyl insulation. Three quarters of an inch of insulation is stripped; the exposed wire is lightly tinned with solder to stiffen it. The tinned end of the lead wire is threaded into the lumen of an 18 gauge hypodermic needle which has been inserted through the walls of the well along a diameter about 0.25 cm. from either end. The needle is removed, leaving the wire clasped by the rubber wall of the well. A cross wire is then inserted in the same plane in a similar manner. The two wires are soldered where they cross; in this way the lead wire is firmly anchored to the well. The exposed uninsulated tips of the wire are clipped just beneath the external surface of the well. (This was not done for the electrode photographed in Fig. 1 in order to show the construction of the electrode better.) The well is cemented to a circular disk of fine mesh cotton gauze 2 inches in diameter (Bay's gauze bandage, 2 inches wide, Parke, Davis and Co.) using undiluted clear rubber cement (Sanford Ink Co., Bellwood, Ill.). The gauze covering the center of the well is cut out

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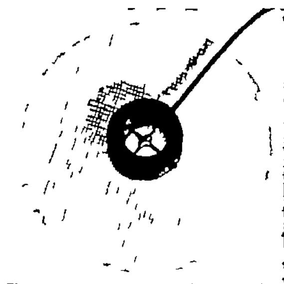


Fig 1 A fluid electrode showing rubber well cotton gauze base and insulated lead wire in the well Contact between lead wire and skin is made by electrode jelly which is not shown

Adhesion of fluid electrodes to skin The method for applying the electrodes to skin should be followed carefully if the electrodes are to perform optimally during activity or for long periods of time or both Fifteen minutes to 24 hours before use the gauze base of the electrode is immersed in rubber cement recently diluted one to one with ether At the same time the upper rim of the well is coated with dilute rubber cement The rubber impregnated gauze base and rim are allowed to dry completely

The site on the skin for the electrode is shaved if hair is present The skin is cleaned thoroughly with ether A thin film of a water soluble deodorant containing aluminum chlorohydroxide (e g ODO RO NO Northam Warren New York) is rubbed into the skin excess deodorant is removed with water and the skin is dried The site is then covered with an even thin film of liquid latex surgical adhesive (DUO Surgical Adhesive Johnson & Johnson) which is gently rubbed into the skin The adhesive is allowed to dry completely or until it is transparent A small hair dryer can be used to decrease the time required for drying skin and adhesive applied to skin The dry rubberized gauze of the electrode is pressed onto the prepared site and an immediate firm bond is produced Latex covering the skin in the well is carefully removed by means of a cotton applicator and ether The well is filled from the surface of the skin to the top of the well with electrode jelly (Cambridge Electrode Jelly Cambridge Instrument Co Inc New York) using a syringe and blunt 15 gauge needle The well is capped with a disk of pliable plastic tape (Scotch Pressure Sensitive Tape No 471 Minnesota Mining and Mfg Co St Paul Minn) which forms an immediate tight seal with the dried rubber cement on the rim of the well Fig 2 shows the electrodes applied to the precordium the electrode over the apex of the heart has been filled and capped A pair of electrodes can be applied in 10 to 15 minutes If heavy sweating is not anticipated the antiperspirant need not be used and this decreases the time required to apply electrodes The electrodes are removed rapidly and easily with ether

Standard electrodes and recorders Direct contact German silver electrocardiographic electrodes measuring 2½ by 1½ inches and slightly curved (Cambridge Instrument Co Inc New York) are referred to as standard electrodes The standard electrodes were applied after vigorous scraping of the epidermis with electrode jelly using a wooden tongue depressor a liberal amount of jelly was left on the prepared side The



Fig 2 Fluid electrodes adhered to skin over the precordium one over the third intercostal space at the left margin of the sternum the other just inferior and lateral to the apex of the heart The upper electrode well has not been filled or capped the lower electrode has been filled with electrode jelly and capped with a disk of plastic tape

standard electrodes were held in place by tightly applied rubber straps

Tracings obtained using fluid and standard electrodes were compared on a direct writing electrocardiograph (Visso Cardiette Sanborn Co Cambridge Mass) paper speed 25 mm/sec 1 mv = 1 cm The same recorder was also used to study the characteristics of tracings obtained with the fluid electrodes on the precordium during various maneuvers For these tracings the electrodes standard or fluid were connected to the recorder by heavy shielded cables used for taking diagnostic electrocardiograms

A direct ink writing polygraph (Model 5 Polygraph Grass Instrument Co Quincy Mass) paper speed 2 5 mm/sec 1 mv = 0 5 cm was used for monitoring R waves during various activities A 6 second signal marker facilitated calculations of minute heart rates during portions of tracing In addition a counter was arranged to simultaneously count R waves as they were traced by the recorder the output of the direct current driver amplifier was coupled through a capacitor to a sensitive relay the relay activated a 115 volt 6 place counter With this arrangement heart rates for prolonged periods of time could be obtained For these records the precordial fluid electrodes were connected to the recorder by unshielded fine lead wires 15 to 20 feet long The recorder and subject were grounded for all tests The ground electrode was usually on the wrist or ankle

Results

Comparison of standard and fluid electrodes using conventional leads In Fig 3 tracings for Leads I and II obtained using standard and fluid electrodes are compared The tracings were obtained immediately after application of the electrodes to the arms and wrists Comparable tracings were obtained at rest During rapid vigorous extension and flexion of the lower arms with the fists tightly clenched spikes were produced by contractions of skeletal muscle these spikes were comparable for the standard and fluid electrodes As would be expected from the type of exercise used tracings obtained with Lead II were clearer than the tracings obtained with Lead I The findings indicate that the fluid electrodes used with standard leads give tracings equivalent to those obtained with standard electrodes For some purposes to be discussed the fluid electrodes used with standard limb leads may offer advantages which make their use desirable

Effect of movement or mechanical shock to electrodes The fluid electrode is pliable and moves freely with the skin Contact between skin and the lead wire is made by a bridge of electrode jelly the thickness and therefore the resistance of this bridge remains about constant during movement of skin beneath the electrode or when the electrode is struck Fig 4,*A* shows a tracing taken using the fluid electrodes on the precordium as shown in Fig 2 A large fold of skin and subcutaneous tissue beneath the apical electrode was lifted and rolled vigorously only slight shifts in the base line occurred In the second portion of the tracing the electrode was hit by multiple sharp blows with a fist small slow spikes resulted which did not interfere with the clear recording of R waves Similar results were obtained using fluid electrodes with standard leads Equivalent manipulations of standard electrodes strapped over the precordium or with standard leads caused marked shifts in the base line or produced tracings unusable even for recording R waves

Thus spikes in electrocardiograms produced by contractions of skeletal muscle are equivalent for fluid and standard electrodes However spikes or shifts in the base line due to movement of electrode and skin are much less pronounced for the fluid electrodes

Monitoring the electrocardiogram to determine heart rates during activity Spikes produced by skeletal muscle can be greatly reduced by using fluid electrodes on the precordium as shown in Fig 4 *B* During the tracing the subject knelt from a standing position did two pushups and rose to a standing position During this exercise movement of skin over the anterior chest and the action of skeletal muscle in the shoulder girdle was considerable in addition the precordium struck the floor twice The base line did not shift the forms of the waves were apparent throughout the tracing and the R waves are clear and undistorted Additional tracings of R waves

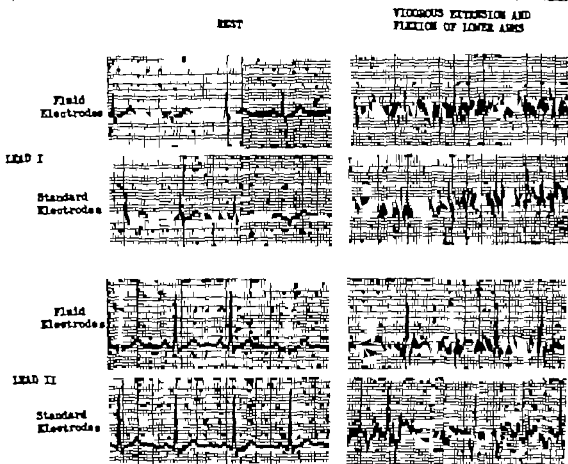


Fig. 3. Comparison of electrocardiograms obtained with fluid and standard electrodes at rest and during activity. The electrodes using conventional Lead I and II were connected to an electrocardiograph; paper speed 25 mm./sec.; 1 mv. = 1 cm. The tracings are equivalent during rest and activity.

during strenuous activity and rest using precordial fluid electrodes are shown in Fig. 4C. The six samples were taken from a single record running for 70 minutes. During the entire record the base line did not shift perceptibly and no spikes which might be mistaken for R waves were recorded. The heart rate ranged from 108 per minute while the subject was jumping to 64 per minute while he was sleeping. The total count for the 70 minutes was 5,099, with an average minute rate of 72. The electrodes had been on the subject for 26 hours when the record was taken. It is apparent from these findings that accurate heart rates can be obtained for long intervals during activity and rest. During the past 2 years we have accumulated over 100 records obtained on males and females using precordial fluid electrodes. The records were obtained about 2 hours, 12 hours, or 24 hours after application of the electrodes. Most of the records ran for 10 to 30 minutes; during each test the subject exercised and rested. The quality of these records was similar to the one demonstrated.

Discussion

The fluid electrodes were developed for a miniature self-contained heart beat counter capable of totaling numbers of heart beats for 24 hours or longer during usual activity.[1] The heart beat counter was activated by R waves. Therefore, electrodes and electrode positions which gave satisfactory electrocardiograms during activity and for at least 24 hours were necessary for the heart beat counter.

With use of the electrocardiograph, vari

ous positions for electrodes over the precordium were tried. When electrodes were placed approximately in the axis of the heart over the base and the apex, the maximum R wave signal was obtained and the configuration of the wave complexes was most consistent from individual to individual. During vigorous exercise of the pectoral and intercostal muscles clear tracings of R waves were obtained.

Various kinds of electrodes were tested during development of the fluid electrodes. Electrodes dependent on conductive glue which became dry when the glue set (e.g. powdered silver suspended in collodion or other adhesives) had to be discarded because of high resistance of the electrode. The high resistance was probably due to dry epidermis acting as a barrier or insulation between the conductive electrode and the tissue fluids of the dermis.

Small silver disks similar to conventional electroencephalographic electrodes were used with electrode jelly. So long as contact between electrode and skin was firm, tracings equivalent to those presented for the fluid electrodes were obtained. Thus we can confirm findings recently reported using electroencephalographic electrodes applied over the manubrium and xyphoid for recording electrocardiograms during exercise.[3] However, methods sufficient for maintaining firm uniform contact between the electrode and skin for 12 or more hours produced severe local inflammation.

Many years ago, heart rates during activity were obtained over periods as long as 24 hours by monitoring R waves picked up from precordial electrodes.[4] In these studies small metal cups filled with a conductive jelly were held in place by rubber straps which encircled the chest

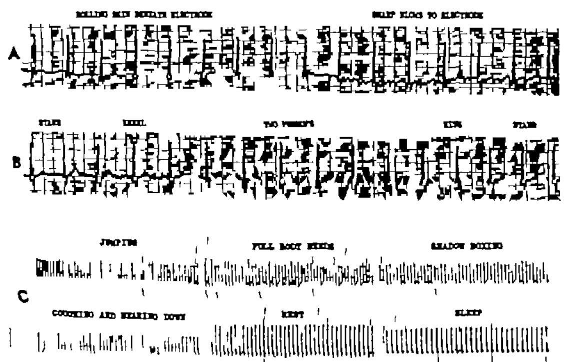


Fig. 4. Electrocardiograms obtained with fluid electrodes on the precordium. *A* and *B*. Tracings obtained with an electrocardiograph, paper speed 25 mm./sec., 1 mv. = 1 cm., show stable base line, small slow pulses produced by direct blows to an electrode, and fast small spikes produced by skeletal muscle during physical activity. *C*. Tracings obtained with ink writing recorder, paper speed 5 mm./sec., 1 mv. = 0.5 cm., taken during … activities, show stable base line and clear recording of R waves. Tracing of 6-second signal marker not shown. Heart rate ranged from 108 per minute while the subject was jumping to 64 per minute while he was sleeping.

Although we did not test this type of electrode we would not expect it to offer advantages over the electroencephalographic type of electrode except that drying out of electrode jelly might be less of a problem. We found rubber strips for holding electrodes in place much too encumbering and uncomfortable for our purpose.

Recently another electrode using a bridge of electrode jelly between skin and metal pickup was described;[4] it was referred to as a *fluid electrode* and we believe this is a suitable designation for various electrodes having this feature. Although our electrodes were developed independently, arguments in favor of using a bridge of conductive fluid between skin and metal pickup were presented in studies made many years ago.[6] Conductive jelly probably penetrates the insulating barrier of the epidermis. (Vigorous rubbing or scraping of the epidermis with abrasive incorporated in some commercial electrode jellies accomplishes this rapidly.) Electrode jelly has this function with standard or fluid electrodes. For standard electrodes, motion of the metal electrode relative to the skin changes the effective electrode resistance appreciably. For the fluid electrodes, the suspension of the metal pickup in a well of conductive jelly permits considerable movement of skin and electrode without producing appreciable changes in resistance.

The fluid electrodes do not cause discomfort and do not restrict activity. Subjects have worn the electrodes for 72 consecutive hours during hot humid weather; each day the subjects played tennis for an hour and took showers. The electrodes functioned perfectly during the entire period, as indicated by continuous operation of the small heart beat counter worn by the subject and by periodic checks using a direct writing recorder. In preliminary studies done elsewhere, the electrodes have functioned well on men sweating heavily, wearing protective clothing, and walking or running on a treadmill.[7] In our laboratory, 2 subjects have each worn the fluid electrodes for 24 hours on 20 or more occasions, 4 subjects have worn the electrodes for 24 hours on 2 or more occasions, and 11 subjects have worn the electrodes for 24 hours. In no instance was irritation or sensitivity to the adhesive apparent.

The small area of skin exposed to electrode jelly was slightly erythematous and indurated after 24 hours; this inflammation disappeared rapidly and completely within a few hours after the electrodes were removed.

Information on series electrode-skin impedance is necessary or desirable for some applications using low impedance amplifiers. Impedance for precordial fluid electrodes was measured on 12 subjects immediately and 2, 4, and 24 hours after application of the electrodes. Values varied from 21 000 to 110 000 ohms immediately after application. The impedance dropped considerably within 2 hours and in most instances remained quite constant for the remaining test period. At 24 hours values ranged from 2 000 to 60 000 ohms; in general, values were highest for older women and lowest for young adult males.

The fluid electrodes have been used with conventional limb leads on patients undergoing cardiac operations. In these cases the electrocardiogram was monitored for at least 24 hours and it was particularly important that the electrodes function properly while the patient was draped and electrodes were inaccessible. The fluid electrodes remained firmly attached and functioned properly on all patients undergoing cardiac operation; the tracings showed distinctly less noise than had been seen when standard electrodes were used. Strips or tape used to hold conventional electrodes may interfere with administration of intravenous fluids on these or other patients undergoing operation; use of the fluid electrode eliminates this difficulty. In other applications the fluid electrodes might be used with conventional precordial leads to record serial electrocardiograms on patients with myocardial infarction, arrhythmias, or other conditions in which it might be desirable for electrodes to remain in place for 3 or more days.

Summary

The construction of a fluid electrode and the method for adhering the electrode to skin is described in detail. The electrode is atraumatic, not encumbering, and remains attached to the skin for long periods of time during strenuous activity. It was demonstrated that the electrical signal

picked up by the electrode is not distorted appreciably by movement of skin beneath the electrode or by direct blows to the electrode

Equivalent electrocardiograms are obtained with fluid and standard electrodes using conventional leads on subjects at rest It is suggested that the fluid electrodes used with conventional leads may have application for monitoring the electrocardiogram in unusual circumstances for example on patients during and after cardiac operations

When fluid electrodes are used on the precordium electrocardiograms showing good electrocardiographic complexes during vigorous physical activity are obtained Use of precordial fluid electrodes for determining pulse rates during various activities and/or for prolonged periods of time is described Other possible applications for the precordial fluid electrodes are suggested

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Case report

Sarcoid of the myocardial septum with complete heart block
Report of two cases

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The sudden onset of syncope due to complete heart block or aberrant ventricular conduction in patients who previously were reported to be entirely well imposes an intriguing challenge for the clinician In the majority of patients in the older age group these arrhythmias are seen usually in hypertensive rheumatic and especially in arteriosclerotic heart disease A diagnosis of Boeck s sarcoid involving the heart is rarely made during life Since the 29 cases of myocardial sarcoid compiled and reviewed by Peacock there have been several more reports of sudden death in patients with sarcoidosis in whom nodular infiltrates strategically located in the myocardial septum resulted in the death of the patient [1,2] The present two cases represent previously unsuspected fulminating disease of the myocardial septum in two patients in the older age group who at autopsy had relatively insignificant sarcoid involvement elsewhere in the body They had lived less than a mile apart most of their lives had been previously in excellent health were admitted to the hospital and died within 2 weeks of each other

Case reports

Case 1 M M a 51 year-old white housewife who was known to be hypertensive but who had no history of rheumatic fever diphtheria or syphilis was admitted to the hospital with a 4-day history of syncopal attack After the fi 3 m this previously she had had one episode of syncope without neurological sequelae but there were no subsequent attacks until 3 weeks before admission when she again fainted without warning she awakened seconds later and was are of a facial flush but no headache palpitations or chest pain There had never been history of chest pain cough or exertional dyspnea although she slept on two pillows and had noted some ankle edema for the past year During the 4 days prior to admission the syncopal attacks had increased in frequency but recovery from each episode had been complete and she continued to feel as well as usual A blood pressure reading taken by another physician earlier in the month was recorded as 160/95 mm Hg the pulse at that time was regular at 90 per minute The patient had been obese for many years had had four pregnancies which were uneventful except for the second during which there was some question of toxemia

Physical examination revealed an obese woman who was comfortable The blood pressure was 175/65 mm Hg pulse was 40 and regular There was venous distention in the neck up to the angle of the jaw at 30 degrees supine and definite though irregular cannon or giant atrial waves could be seen The carotid pulsations were collapsing but small Fundi were normal Diaphragmatic excursion was poor and there was some decrease in breath sounds with a few fine rales in the left lower lung field The heart was slightly enlarged to the left with bradycardia at 40 per minute and definite variation in the intensity of the mitral first sound A Grade 2 systolic ejection type of murmur was present at the base and heard at the apex poorly referred to the neck The second pulmonic sound was slightly accentuated and normally split There were no organs or masses palpable in the abdomen and there was some brawny edema of the feet

LABORATORY EXAMINATION Hemoglobin was 13 Gm Hematocrit was 44 per cent The white blood cell count was 8 500 with slight shift to the left

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Fig. 1. Case 1. X-ray films of the chest showing congestion of the lung fields, marked prominence of the hilar areas, and large flocculent areas of increased density behind the heart in the lateral view.

Blood sedimentation rate was 30 mm./hr. VDRL was negative. Blood urea nitrogen was 21 mg. per cent. Urinalysis negative. Three serum transaminases were normal. Sodium was 140 mEq./L., potassium 4.1 mEq./L., chloride 97 mEq./L., carbon dioxide 29 mEq./L. Sputum culture showed normal flora 2+, pneumococci 4+; sputum was negative on smear and culture for acid-fast bacilli. PPD was 1:1 negative. Serum protein was 7.2, albumin 4.1, globulin 3.1.

Chest x-ray examination showed some congestion in the lung fields with unusually prominent hilar structures and a small wedge-shaped area of pneumonitis extending into the right base. There were several flocculent densities behind the heart in the lateral view. The cardiac silhouette was globular in contour and the right atrium was prominent. There was no fluid in the pleural spaces (Fig. 1).

The electrocardiogram recorded at the time the patient was admitted to the hospital showed third-degree heart block with idioventricular rhythm at a rate of 40 (Fig. 2 *left*).

HOSPITAL COURSE. The patient was placed on coronary precautions and treated with bed rest, Mercuhydrin, tetracycline, and mild sedation. She ran a remittent fever to 100.6° F. daily around noon and diuresed 7 pounds in the first week. Her electrocardiogram showed reversion to sinus rhythm at 85 per minute with frequent premature contractions and left bundle branch block (Fig. 2 *right*). She appeared to be comfortable and was asymptomatic during laboratory studies and the recording of subsequent electrocardiograms. Her condition appeared to be satisfactory and she was digitalized slowly and put on a low-sodium diet. Although she had had no chest pain, septal infarction was considered to be a possibility which might explain the changes in the electrocardiograms and for this reason she was placed on anticoagulants.

She had no further episodes of syncope until the thirteenth hospital day when she complained of feeling weak and dizzy and slightly nauseated. Blood pressure was not obtainable and her pulse was 24. She was deeply cyanotic, out of contact, and gasping for breath with white froth about the mouth. Sublingual Isuprel had had no effect. When the cardiac pacemaker was applied the pulse and respiration returned immediately and when withdrawn the heart assumed an idioventricular rhythm with a rate of 38 per minute. The electrocardiogram was identical to that taken at the time of her admission to hospital. Her color returned to normal within 1 minute and she responded in about 10 minutes. She was then given 0.3 c.c. of 1:1000 adrenaline and 10 mg. of sublingual Isuprel. An hour later the patient was alert and responsive and appeared to be entirely normal. She was placed on 50 mg. of ephedrine which was alternated with 10 mg. of Isuprel sublingually every 2 hours and her pulse became full and regular but at a rate of 30 per minute. Three hours after the initial episode she again lost all blood pressure and pulse and her respiration ceased. The pacemaker was applied but there was no response. Intracardiac adrenaline was given with no response and she expired quietly.

PATHOLOGY. Autopsy was limited to the heart. The heart was somewhat enlarged and focally involved by very small firm homogeneous gray white nodules which were especially prominent in the septal area and which in the upper portion coalesced to form a solid mass in the region of the conduction bundle (Fig. 3). There was some pulmonary congestion but no pleural effusion. Pleural surfaces and lymph nodes of the lung were also

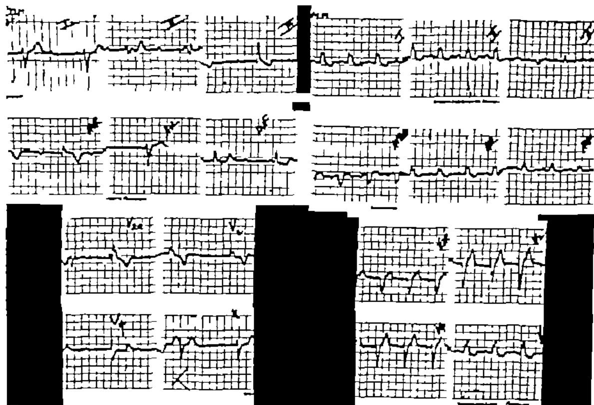


Fig 2 Case 1 *Left* Electrocardiogram taken at the time the patient was admitted to the hospital showing complete heart block with idioventricular rhythm atrial rate 88 ventricular rate 36 *Right* Spontaneous reversion after 4 days to sinus rhythm with left bundle branch block

involved by these small plaques of grayish white tissue tending to be flat in outline and proving on microscopic section to be sarcoid No caseation was present and no acid fast bacilli or fungi were found

Case 2 J P 76-year-old white housewife had been in perfect health while working 5 days a week and taking in laundry besides Six and 3 days prior to her admission to the hospital she had syncopal attacks without warning these attacks were followed by a flush but no headache palpitation chest pain nor dyspnea On the day of admission there had been a succession of episodes of unconsciousness these had resulted in falls which produced several bruises of the face arms and legs There was no history of head injury convulsions diabetes or hypertension

On physical examination the blood pressure was 2?0/?0 mm Hg She had a regular pulse of 40 per minute She appeared to be in no distress and even protested examination She was obese had a sallow complexion but was not cyanotic. Fundi showed Grade II arteriosclerotic changes There were cannon atrial waves which could be seen easily in the neck but no venous distention A few crackling râles were heard at the right base posteriorly There was no cardiomegaly A Grade 3 high pitched pansystolic apical murmur could be heard referred to the axilla The second pulmonic sound was not accentuated and there was a third heart sound at the apex but no diastolic murmur The liver was palpable one fingerbreadth and there was no peripheral edema

LABORATORY EXAMINATION Hemoglobin was 10 0 Gm Hematocrit was 37 per cent White blood cell count was 10 000 with normal differential The serum transaminases were normal Urinalysis showed 1 019 3+ protein 2+ but blood cells Sodium was 132 mEq /L potassium 7 2 mEq /L chloride 98 mEq /L carbon dioxide 23 mEq /L Total protein was 6 2 Gm per cent albumin 3 1 globulin 3 1

The electrocardiogram taken at the time the patient was admitted to the hospital showed third degree heart block with premature ventricular contractions which occurred at times as bigeminal rhythm (Fig 4)

HOSPITAL COURSE In view of her age and the sudden onset of symptoms and despite the lack of chest pain the patient was treated for myocardial infarction Because of her syncopal episodes she was started on ephedrine 25 mg and sublingual Isuprel 10 mg alternating at 3 hour intervals Her pulse varied between 3? and 40 and her blood pressure dropped to 140/40 mm Hg but she felt well and experienced no chest pain An increase in the Isuprel to 20 mg every 6 hours alternated every 3 hours with 25 mg of ephedrine produced no increase in heart rate or side reaction On the fifth hospital day she had a sudden episode of asystole which did not respond to Arenalone There



Fig 3A Case 1 Gross pathologic specimen showing the cavity of the left ventricle aortic valve and septum on the left Note the lighter shaded tongue of sarcoid in the upper portion of the septum

as rapid succession of three subsequent episodes of ventricular standstill which responded to percussion of the chest and at this time the cardiac stimulator was applied since it was thought that the patient might have septal infarction She was given 100 mg of hydrocortisone intravenously adrenaline molar lactate Demerol and oxygen At first she appeared to respond with spontaneous ventricular activity taking over after the pacemaker was stopped But after 2 hours it was apparent that the post stimulation T waves had flattened and there was at last no spontaneous ventricular activity after the stimulator was withdrawn The P waves however continued alone for a considerable time with occasional bizarre ventricular ectopic contractions and she expired quietly

AUTOPSY There was no excess fluid in the pericardial sac and the pericardium showed no adhesions The heart weighed 450 grams It was hypertrophied and dilated The right ventricle measured 0 cm the left ventricle 1 2 cm The myocardium was particularly peculiar in that the septum itself had been almost completely replaced by white homogeneous firm tumor tissue which appeared to extend the width of the septum and into small part of the left ventricular wall at the apex On microscopic section this tissue proved to be sarcoid (Fig 3) There was also a small infiltration about the left circumflex coronary artery in the epicardium There was an old occlusion of the anterior descending branch of the left coronary All the heart valves were unremarkable There was no evidence of emboli or recent infarction The pleural surfaces of the lungs were smooth and glistening without evidence of adhesions but there were numerous white implants the largest of which measured 2 cm over the right lung There was some edema and atelectasis of the lower lobes bilaterally and some parenchymal implants of the tumor also Several hilar nodes which contained tumor tissue were present The capsule of the spleen was thick ened with white firm fibrous tissue and was dark red in color with pale tan nodules within the parenchyma The gastrointestinal tract pancreas and kidneys were unremarkable The liver had yellow white nodules throughout the parenchyma similar to those in the spleen and the capsule was mottled with white speckles of tumor There was an adrenal cortical adenoma The brain was symmetrical with slight atherosclerosis of the cerebral vessels and no focal lesions

Comment

Both patients were treated initially as though they had had myocardial infarctions In the first case sarcoid was suspected only after the patient became well enough to risk having a chest film made and the features of her history and hospital course appeared unusual for coronary disease Her electrocardiogram showed reversion to normal sinus rhythm after 4 days although no steroids had been used Immediate treatment of her heart block was imperative and in spite of large doses of ephedrine Isuprel and adrenaline there was not an adequate ventricular response In the second case the suspicion of sarcoid was academic in view of her *fulminating* course and complete lack of response to all



Fig 3B Case 1 Septal myocardium Microscopic section through the superior portion of the bundle of His which is now completely infiltrated with granulomata typical of sarcoid

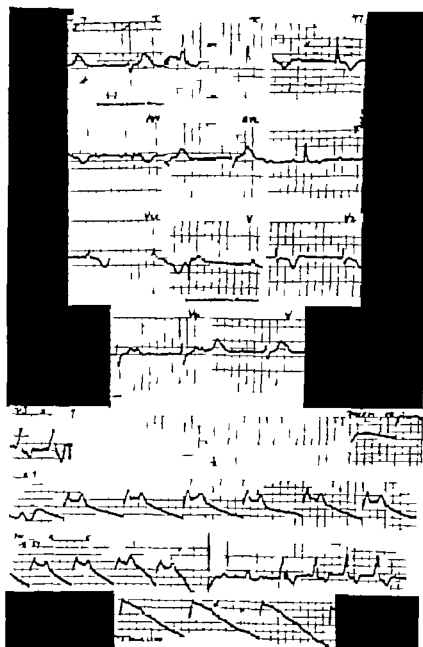


Fig 4 Case Electrocardiogram bowing (at top) complete heart block trial rat 98 entricular rate 36 Bot om Lead II tracings depict idios entricu lar rh thm w th widened QRS entricular stand till with continu ng I w es entricular cc tractions on the pacemaker w th resumption of spontaneous tricular actn ty and finally recurrent entricular arrest with persistent trial activity while on the pacemaker Note that the poststimulation T es (arrow) ha e dimini hed markedly

available therapeutic measures There was little time for x ray examination or diag nostic studies Although the diagnosis of myocardial sarcoid was again uspected from the obvious imilarity to the hospital course of the previous patient confirmation at autopsy was till surpri ing

There was a notable lack of response to all the usual cardiac drug stimulants On the pacemaker she appeared to do well at first and spontaneous ventricular rhythm resumed after short periods of stimu lation (Fig 4) Soon it became necessary to increase the voltage of the stimulator



Fig 5A Case 2 Pathologic specimen Cut sections through the myocardial septum showing almost complete replacement of myocardium with the pale tan fibrous like infiltration

markedly in order to obtain any ventricular response and it was noted that even with contraction the poststimulation T waves became less and less prominent It was interesting that the P waves continued unabated both during ventricular activity and long after it had stopped There was an occasional bizarre ventricular complex but no conducted beats

The striking features of these cases were the specificity of sarcoid involvement of the highly specialized conduction bundle in the ventricular septum with minimal sarcoid lesions found elsewhere at postmortem It is a wonder in view of the pathologic specimens that any transmission of impulses had been possible through the ventricular septa of these two patients because the width of the superior part of the septal myocardium was almost completely replaced by sarcoid tissue It was also quite remarkable that both patients had been apparently well as few as 5 days before hospitalization and followed each other so closely in almost identical courses Furthermore they both suffered from what has been considered to be a rather rare manifestation of a moderately common systemic disease

Of the 29 cases of myocardial sarcoid reviewed by Peacock and associates 15 either were described as Stokes Adams disease or showed clinical evidence of heart block Longcope and Freiman[8] have previously cited the incidence of myocardial involvement in 92 autopsied cases as 20 per cent It has become recognized with increasing frequency however that in those patients in whom death has been due to sarcoid the heart frequently is found to be infiltrated by the nodular tubercle like lesions As evidence of this involvement tachycardias ventricular extrasystoles and other cardiac arrhythmias in addition to heart block have been reported The duration of clinical sarcoidosis before death due to myocardial involvement has been cited as varying between 3 months and 15 years and the diagnosis of myocardial involvement has usually been made at autopsy



Fig 5B Case 2 Microscopic section through [illegible] seen in Fig 5A showing replacement by sarcoid granulomata

The absolute unpredictability of involvement of organs is well known in that some patients have severe involvement of one organ system with complete absence of lesions in another. In the majority of cases reported with or without heart block there has usually been extensive infiltration of sarcoid into the myocardium involving the left ventricle septum apex papillary muscles and including diffuse miliary sarcoid granulomata throughout the myocardium and epicardium.[11,13]

These two cases bear the greatest resemblance to the case reported by Simpkins[10] in which the largest patch involved the entire thickness of the septum in the region of the atrioventricular bundle. They are unique from other cases in the literature however in that the myocardial involvement of these two cases was almost exclusively septal and miliary implants in other organs were not extensive. It was obvious from the autopsy studies that had the nodular infiltrations of sarcoid not involved the heart so strategically both patients might have been well for some time to come. In addition experience with therapy here has been similar to the general experience reported with myocardial sarcoid in that the outcome was rapidly fatal in spite of known therapy including steroids.

Conclusions

Two cases of myocardial sarcoid with complete heart block have been reported. They were unique in that involvement was limited almost exclusively to the septum and remarkable in the coincidence that both patients had been well as few as 5 days before hospitalization and followed identical rapidly fatal courses within 2 weeks of each other.

I wish to thank Dr George McAdam for his help with the slides of the pathologic specimens.

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Review

The vasodilator nerves

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The subject of vasodilator nerves is a facet of circulatory physiology which stands in some need of clarification. Although current textbooks contain fairly definite statements and elaborate schemata on vasodilator nerves and their functional significance, close scrutiny reveals these descriptions to be of doubtful validity. In the first place, they are frequently based on assertions contained in a few early papers and reiterated, more or less uncritically, throughout several decades. The most frequently cited of these papers are from the turn of the century.

All early studies and several recent ones are based on plethysmography and other indirect methods of recording blood flow. Some of the confusion which prevails within the vasodilator field is undoubtedly due to misinterpretation of results obtained by these means. Authors have not always taken into consideration the fact that a vasodilator response initiated via nerves does not prove the existence of a vasodilator nerve. Vasodilatation can be due to inhibition of prevailing vasoconstrictor tone (e.g., via baroceptor activation or local reflex arcs) or it can be secondary to metabolic processes in an activated organ (e.g., a gland or muscle).

The belief in authorities and the consequent perpetuation of old arguments, as well as the use of outmoded techniques of recording, have retarded development within the vasodilator field as compared with that in other areas of circulatory physiology. However, recent years have brought some progress, and although our knowledge is still too fragmentary to permit definite statements on the functional significance of recently acquired data, a few remarks may be justified. They should be regarded, however, as an expression of personal views and not as finally valid.

General remarks on vasomotor innervation

It is interesting to note that all assertions in regard to the vasodilator nerves and their function have been made despite the fact that—in so far as I am aware—no vasodilator fiber or vasodilator nerve impulse has yet been anatomically or electrophysiologically identified. Vasodilator fibers in nerve trunks are intermixed with other fibers, somatic or autonomic, and cannot be isolated by the techniques available. Presumably they belong to the thin unmyelinated fibers, but this fact does not serve to facilitate their identification. Experimental evidence concerning the existence of vasodilator nerves is thus indirect; conclusions are drawn principally from vasodilator responses elicited by stimulation of peripheral mixed nerves. Recently, vasodilator responses have been induced by topical stimulation of vasodilator pathways in the brain and by reflex activation of vasomotor structures in conscious animals and in man. The validity of the conclusions drawn from these experiments will be discussed below.

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Conclusions

Two cases of myocardial sarcoid with complete heart block have been reported; they were unique in that involvement was limited almost exclusively to the septum and remarkable in the coincidence that both patients had been well as few as 5 days before hospitalization and followed identical rapidly fatal courses within 2 weeks of each other.

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vasodilator fibers have on the whole no *functional connections* with the central nervous system [3,4]

Sympathetic vasodilator nerves

According to current literature sympathetic vasodilator nerves in cats and dogs are distributed to skeletal muscles facial muscles and the buccal mucosa to the coronaries of the heart the intestines and certain areas of skin such as the ear of the dog [5] In man sympathetic vasodilator nerves have been discussed mainly in connection with the skin and skeletal muscles As regards the chemical transmission of vasodilator impulses the sympathetic vasodilator nerves have been thought to be adrenergic cholinergic and noncholinergic

Accumulated data now indicate that peripheral distribution of sympathetic vasodilator nerves is much simpler than was previously assumed In a series of investigations Swedish workers found cogent evidence of the distribution of such nerves to the skeletal muscles only (in cats and dogs) Furthermore the results pointed to acetylcholine as the sole transmitter of sympathetic vasodilator effects [6] This finding promoted the development of their studies because it became possible to distinguish between vasodilatation due to activation of vasodilator nerves and vasodilatation due to inhibition of vasoconstrictor tone the former type was blocked by atropine but the latter remained uninfluenced Sympatholytics (as well as reserpine which empties the vasoconstrictor nerves of their transmitter substance noradrenaline) abolished vasoconstrictor tone and thus vasodilatation due to its inhibition but not vasodilatation due to vasodilator impulses (Table I) Of course such a pharmacologic analysis is far from ideal but in the absence of electrophysiologic or other means of identification it must suffice

Now that a way had been found to identify vasodilator effects due to activation of sympathetic vasodilator nerves it was possible to study the latter's representation in the central nervous system In a series of investigations the intracerebral course of a sympathetic vasodilator pathway was traced Originating from the motor cortex it passed via the hypothalamus and the collicular region through the ventrolateral part of the medulla oblongata down to the spinal lateral horns [10] (Fig 2) The vasodilator tract appears to have relay stations at least in the hypothalamus and the collicular region since neither chronic decortication[10] nor chronic supracollicular decerebration[11] abolish vasodilator responses due to hypothalamic and bulbar stimulation Of particular interest in the further discussion is the fact that the medullary *part of the outflow has no demonstrable* anatomic and functional connections with the previously elucidated vasomotor structures in the rhomboid fossa Stimulation

Table I Remarks on the physiology of the dual vasomotor innervation of the skeletal muscles (in dog and cat)

Sympathetic vasoconstrictor nerves	*Sympathetic vasodilator nerves*
Postganglionic fibers adrenergic	Postganglionic fibers cholinergic
Exert tonic influence on the vascular bed	Exert no tonic influence on the vascular bed
Increase in activity yields vasoconstriction decrease vasodilatation	Increase in activity yields vasodilatation
Vasodilatation blocked by sympatholytics and reserpine	Vasodilatation enhanced by eserine blocked by atropine
Depressor reflexes evoke vasodilatation due to vasoconstrictor inhibition	Depressor reflexes do not activate vasodilator nerves
Vasodilatation due to vasoconstrictor inhibition leads to increased uptake of oxygen in skeletal muscles of anesthetized cat	Vasodilatation due to vasodilator decreased uptake of oxygen in anesthetized cat

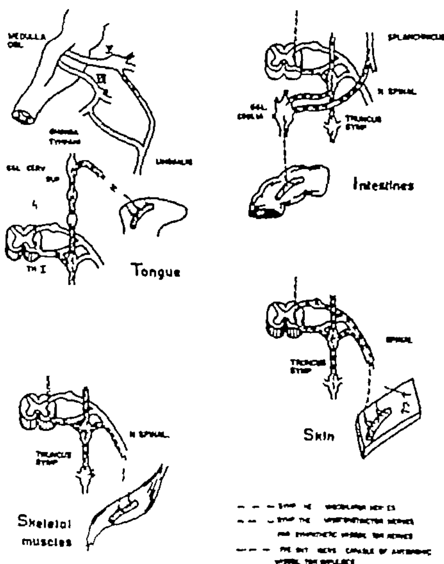


Fig. 1. Vasomotor innervation in different areas.

The vasoconstrictor nerves form anatomically and functionally an extensive and well integrated part of the vasomotor innervation. A centrally governed vasoconstrictor outflow covers the entire peripheral vascular bed and regulates, via a continuous flow of impulses, the tone of the resistance and capacitance vessels.[1] Central or spinal vasomotor reflexes bring about changes in vasoconstrictor tone and consequent alterations in peripheral resistance and blood flow. Practically all known vasodilator reflexes, as will be seen, result from inhibition of vasoconstrictor tone.

The vasodilator nerves constitute neither anatomically nor physiologically a homogeneous group. They are conventionally divided into three main groups: the sympathetic, the parasympathetic, and the dorsal root vasodilator fibers. They innervate certain restricted vascular areas which thus have a dual vasomotor innervation, vasoconstrictor and vasodilator (Fig. 1). Some vessels, such as those in cutaneous and splanchnic regions, apparently lack centrally controlled vasodilator nerves; at least the evidence of a vasodilator innervation to those areas is not very convincing.[2] The vasodilator nerves, in contrast to the vasoconstrictor nerves, have no common integrating structures in the central nervous system. The dorsal root

trolled by a hypothalamic defense center. Vasodilator reactions have been observed to occur in the skeletal muscles of human beings in response to psychic stress (difficult arithmetic, alarming reports, startling sounds, etc.).[15,17] Such responses were reported to disappear after atropine.[18]

Ascribing to the sympathetic vasodilator outflow a functional role in emergency and other emotionally tinged reactions accords with the current view of the hypothalamus as a relay station which integrates the autonomic and somatic responses which occur in various affective reaction patterns. Pending more conclusive data, however, any interpretation must be tentative. The structure of the hypothalamus is complex, and stimulation with electrodes is apt to activate many neurons which may not be functionally related. No emergency responses were seen in dogs in which the hypothalamus was stimulated, although perhaps the corresponding neurons were blocked by the anesthesia. In any event, it seems unlikely that the functional significance of the vasodilator outflow is limited to emotional behavior reactions. The representation in the motor cortex as well as the selective distribution to the skeletal muscles raise the question whether or not the vasodilator fibers are concerned in *muscular activity as such*. It is assumed, for instance, that initial and even anticipatory circulatory readjustments occur with muscular exercise. However, that muscular exercise does not require vasodilator nerves *is indicated* by the fact that no impairment of blood flow in muscles or of working capacity has been observed after sympathectomy.

Further speculation in regard to the functional significance is rather pointless, *I think, until* we ascertain the real meaning of the vasodilator responses. Where do the vasodilator impulses act? Do they open up capillaries or shunts? In order to settle these questions the influence of changes in blood flow on the clearance of radioactive material (from an intramuscular depot (in cat gastrocnemius)) was investigated.[19] Reduction and augmentation of blood flow by mechanical, nervous and pharmacologic means caused, with one exception, corresponding qualitative changes in the clearance of radioactive isotopes. Increase in blood flow due to activation of the sympathetic vasodilator outflow was not accompanied by any increase in radioiodide clearance. It remained unchanged. If any conclusion is justified by these clearance studies, it is that the vasodilator nerves do not open up new capillaries, for if they did so, the clearance should have increased. It could be that the increased blood flow was directed through some kind of shunt flow.

Whether or not arteriovenous shunts occur in the muscles has long been debated. Thinking that concomitant recording of blood flow and oxygen consumption might bring to light some new considerations, we calculated oxygen uptake in skinned hind limbs of cats from the difference between the arterial and venous oxygen saturations as well as the blood flow.[3] To our surprise, the increase in blood flow produced by vasodilator activation led to a diminished uptake of oxygen. On the other hand, a corresponding increase in blood flow induced by vasoconstrictor inhibition was followed by *an elevated uptake* of oxygen. It is not easy to interpret these findings. The decrease *in uptake of* oxygen during vasodilator activation could signify either a reduction in the metabolic requirement for oxygen in the muscles or interference with the diffusion of oxygen to the muscle. Since we have no experimental evidence in favor of the first alternative, the second seems more acceptable. Here again various possibilities must be considered. The blood may be diverted from capillaries to paracapillary vessels that provide less opportunity for diffusion of oxygen. Although arteriovenous anastomoses have been directly observed in skeletal muscles, it is doubtful whether they play a significant role in muscular blood flow. Not even under activation of the sympathetic vasodilator nerves do more than a percentage or so of spheres with a diameter of 20 μ pass through a muscle.[21] The calibers of shunts, if they exist, should not be appreciably different from those of true capillaries. A *shift in the* capillary flow with a reduced *transcapillary* distance or an accelerated linear velocity of the blood could serve *to reduce* diffusion of oxygen. An observation which may useful in this context is that vasodila

activation is accompanied by reduced uptake of oxygen even in reserpinized animals—when in other words the vasoconstrictor outflow is defunctionalized because of a lack of a vasoconstrictor transmitter. Therefore the increase in the intramuscular blood flow must be ascribed solely to vasodilator activity. In the light of available data it seems reasonable to assume that the reduced uptake of oxygen during vasodilator activity is due to the opening up of shunts—anatomic or physiologic—in the muscles or to a yet undefined shift of blood flow within the capillary bed.

The increase in uptake of oxygen during vasoconstrictor inhibition, having been rather unexpected, calls for some comment. It is presumably attributable to the fact that the skeletal muscles in an anesthetized animal are partially anoxic. That there is a slight production of lactic acid is evidenced by the augmented content of lactic acid in the venous outflow. Opening up of the capillary flow by vasoconstrictor inhibition remedies the prevailing oxygen deficit, as manifested by an increased uptake of oxygen.

The preceding observations on radioactive clearance and uptake of oxygen in the muscles have been treated in some detail since they represent in effect the first attempts to elucidate the functional significance of vasodilator impulses. Although the findings do not, unfortunately, afford much insight into the part played by the sympathetic vasodilator nerves, they do indicate that vasodilator nerves may serve specific purposes in the innervated organs.

Even with maximal activation of the sympathetic vasodilator outflow the increase in muscular blood flow amounted to only 4 or 5 times the basal level, seldom more. A maximal opening up of the capillary bed in a resting muscle ought to result in a considerably greater flow of blood.

When the vasodilator response in the muscles was blocked by atropine a previously hidden vasoconstriction not infrequently appeared. This was indicated by a decrease in muscular blood flow. And in accordance with this observation we noticed in some of our clearance experiments that sympathetic vasodilator activation not only did not cause any increase in clearance but in some experiments actually reduced it. Furthermore activation of the vasodilator outflow by hypothalamic, mesencephalic, or medullary stimulation led to a concomitant discharge of adrenaline in amounts great enough to have metabolic effects. In fact, an increased output of lactic acid was observed in the venous blood from the skeletal muscles.

Whether this pattern of response to intracerebral stimulation has any physiologic significance is quite obscure, but at a recent symposium I could not resist the temptation to suggest that activation of the sympathetic vasodilator outflow might be part of a reaction pattern elicited in situations in which, for one reason or another, the animal has to conserve its resources of oxygen.[22]

The hemodynamic consequences of the vasodilator activity need to be discussed. A general vasodilator activation in the skeletal muscles causes a considerable decrease in the total peripheral resistance in the circulatory bed. This is compensated by the concomitant vasoconstrictions in the skin and splanchnic regions. If such compensatory vasoconstrictions are interfered with, vasodilator activation is accompanied by a fall in blood pressure. And on the other hand, if the vasodilator responses are abolished by atropine, no pressure effect appears. It is conceivable, therefore, that vasodilator activation may serve as a stabilizing and compensatory *hemodynamic factor in circumstances in* which intense activation of sympathetic adrenergic outflow to the heart and the vascular bed would lead to an undesirable rise in blood pressure. Such a situation may occur in the initial stage of, or anticipatory to, muscular exercise. The output of the heart increases abruptly, and vasoconstriction is supposed to occur in cutaneous and splanchnic areas simultaneously with emptying of the blood reservoirs and the capacitance vessels. Unless some low-resistance channels are opened up, an increase in circulatory volume of the output of the heart and in the peripheral resistance will lead to a rise in blood pressure. The vasodilator nerves might serve as moderators of the peripheral resistance in the muscular circulation during the initial stage of muscular activity. This and other sug-

gestions as to the functional significance of the sympathetic vasodilator nerves to the skeletal muscles are so far purely speculative.

The sympathetic outflow to the heart is thought to contain vasodilator fibers to the coronaries. There is little experimental evidence to support this assumption, which is based mainly on the observation that the coronary blood flow increases when the stellate ganglion or the cardiac sympathetic nerves are stimulated. Circumspection is required in the interpretation of these observations, for stimulation of the sympathetic nerves to the heart may accelerate the heart rate and raise the contractile force of the heart, thereby increasing the metabolism of the heart muscle. This in itself will increase the coronary blood flow. However, the sympathetic nerves to the heart contain cholinergic fibers, and according to recent reports stimulation of cholinergic vasodilator fibers is possible without concomitant activation of adrenergic inotropic and chronotropic fibers. The functional significance of the assumed sympathetic coronary vasodilator fibers remains to be elucidated.

The sympathetic vasodilator innervation to the human skin has been a much disputed subject. Cutaneous blood flow undoubtedly increases when the body becomes heated and especially when sweating occurs. This increase in cutaneous blood flow was once thought to be due to activation of vasodilator nerves, but current data favor the view that the vasodilatation is secondary to the activity of the sweat glands. Bradykinin is suggested as the vasodilator agent. Some authors still contend that the skin of the upper part of the forearm has a special sympathetic vasodilator innervation.

The parasympathetic vasodilator nerves

Vasodilator fibers were supposed to run in the chorda tympani to the tongue and to the glands of the oral cavity, and in the sacral nerves to the external genitals and possibly the bladder and rectum. This concept was recently modified when it was shown that the increased blood flow through a salivary gland when the chorda tympani was stimulated was secondary to metabolic processes in the activated gland. Bradykinin was held responsible for the vasodilator response. The existence of vasodilator fibers is not, however, ruled out. Further investigations may show the parasympathetic vasodilator outflow to be limited to the tongue and the genitals, where the vascular changes do not appear to be secondary to glandular or other tissue activity. The old view of Bayliss and others that the vagus contains vasodilator fibers is not supported by modern investigations.

Data on the physiologic properties of the parasympathetic vasodilator nerves are still sparse. These nerves are believed, however, to be thin unmyelinated fibers with acetylcholine as the chemical transmitter. In accordance with this view it is claimed that the effect of sacral nerves is blocked by atropine and enhanced by eserine. On the other hand, vasodilatation in the tongue due to stimulation of the chorda tympani is unaffected by atropine.

The functional significance of the parasympathetic vasodilator nerves to the tongue is unknown. The dilator fibers to the genitals are thought to play a part in erection. The parasympathetic vasodilator fibers do not appear to participate in the baroceptor or chemoceptor control of the vascular tone and are probably devoid of tonic activity.

The dorsal root vasodilator nerves

The nineteenth-century observation that stimulation of dorsal roots, mechanical or electrical, elicited an increased flow of blood in the skin, especially of the foot pads, has caused a great deal of speculation as to the functional role of antidromic vasodilator impulses. The latter played a large part in Bayliss' elaborate system of vasodilator nerve control of the peripheral vascular bed. The vasodilator activity in the dorsal root fibers was thought to be governed by a medullary vasodilator center. Subsequent investigations have served to discredit this hypothetical system of Bayliss. The dorsal root fibers afferent as they are lack functional vasodilator connections with the central nervous system.

To judge from the parameters of mechanical, thermal and electrical stimulation, the dorsal root vasodilator fibers belong to the

C fiber group. They are activated by various noxious stimuli and probably are pain fibers. Accordingly, stimulation of the dorsal roots elicits vasodilatation in the skin, which is rich in pain fibers, but little or no vasodilatation in the skeletal muscles, which are poor in such fibers.

Histamine or a histamine-like substance as well as acetylcholine have been regarded as the chemical transmitters. An adenosine triphosphate-like substance has been observed to occur with cutaneous vasodilatation and has consequently been suggested as the transmitter.[28] For the present, however, the transmitter question may be considered shelved.

The functional significance of the antidromic vasodilator impulses may lie in axon reflexes as a facet of the triple response to noxious stimuli. Such stimuli—mechanical, chemical, thermal, inflammatory, etc.—elicit via axon reflexes local reactive vasodilatation as one component of a local cutaneous defense reaction.[12]

General remarks

Current doctrine still holds that vasodilator nerves are functionally coordinated with the vasoconstrictor nerves in the *regulation of vasomotor tone.* This concept can be traced back to Bayliss' papers from about 1900, when—apparently influenced by Sherrington's studies on the reciprocal innervation of the skeletal muscles—he postulated the existence of a similar reciprocal control of the blood vessels.[3] Vascular tone was assumed to be the result of concomitant vasoconstrictor and vasodilator nerve influences on the peripheral vascular bed. The tonic activities in the vasoconstrictor and vasodilator outflows were thought to be governed by medullary vasoconstrictor and vasodilator centers capable of reciprocal interference with each other's activity.

Bayliss further assumed that the medullary vasodilator center exerted a tonic inhibitory influence on the blood vessels. Since he considered sympathetic vasoconstrictor tone to be weak or nonexistent, he was obliged to postulate a centrally controlled *vasodilator outflow* to explain vasodilator reflexes. By discounting the existence of sympathetic vasodilator nerves, he was forced to localize the vasodilator impulse traffic to parasympathetic and dorsal root fibers. Today we know with certainty that (a) the vasoconstrictor nerves exert a tonic influence on virtually the whole vascular bed on both precapillary resistance and postcapillary capacitance vessels, and that (b) the inhibition of vasoconstrictor tone may result in pronounced vasodilatation, especially in regions in which vasoconstrictor tone is high, e.g., the splanchnic, cutaneous, and muscular areas. Therefore, we need not postulate the existence of vasodilator nerves to explain vasodilator effects. The fact is, as pointed out above, that vascular reflexes are, as a rule, the result of diminished vasoconstrictor tone (Fig. 2).

As to the vasodilator nerves, it has been shown repeatedly that the skeletal muscles are supplied with sympathetic (cholinergic) vasodilator nerves. On the other hand, attempts to demonstrate vagal vasodilator nerves to the splanchnic area have failed. There remains no convincing evidence that vasodilator impulses are able to pass antidromically along cerebrospinal pathways via afferent dorsal root fibers to skin or muscles. The idea, in fact, seems rather absurd in the light of accumulated neurophysiologic experience. Accordingly, cutaneous vasomotor reflexes depend on the sympathetic innervation. They remain intact after sensory denervation but are completely abolished by sympathectomy, following which axon reflexes alone persist.

Little remains, therefore, to support Bayliss' vasodilator theory and reciprocal vasomotor innervation hypothesis. On the contrary, nervous vasomotor control appears in reality to be exerted solely via the vasoconstrictor nerves. The vasodilator nerves probably serve specific ends in the restricted areas innervated. The deeper significance of the vasodilator innervation remains to be elucidated.

Closing remarks

This brief review on the vasodilator nerves contains, I am afraid, more destructive than constructive criticism. *If,* however, the new data offered in place of outmoded theories help to revive interest in vasodilator phenomena, *the* principal aim of this article will have been fulfilled.

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Annotations

Reflex vasodilatation in treatment of peripheral vascular diseases

It is too frequently forgotten that among the many therapeutic measures available for peripheral vascular disease one of the most dependable mechanisms for producing peripheral vascular dilatation in the skin and digits is associated with heating of the body. Heating can be more effective than drugs. In medical practice the patient with peripheral vascular disease is simply instructed to wear enough warm clothing to produce slight discomfort and a little sweating. When the patient is outdoors his hands and feet should be properly covered with woolen socks and loose gloves. He should avoid exposure to cooling such as by drafts, dampness, rain and the like. As shown years ago by Lewis[1] and workers, the reflex vasodilatation of the peripheral vessels of the skin occurs when the body is warmed and this dilatation develops in areas usually involved in vascular disease. Whether this reflex dilatation is the result of only inhibition of sympathetic vasoconstriction tone or is due in part also to activity of vasodilator fibers[2] or humoral factors such as bradykinin and vasodilator substances is physiologically important, but from the therapeutic viewpoint it is sufficient that vascular tone is reduced and vasodilatation occurs. This vasodilatory phenomenon should be exploited on its own merit as well as in assistance to vasodilator drugs which may also be of use. Obviously overheating should be avoided if there is cardiac disease or other contraindications. Certainly body warmth should be tried before sympathectomy or sympathetic ganglionectomy is performed. The sympathetic nervous system should be exploited in therapy before the nerve supply to the peripheral blood vessels is irreversibly destroyed by operation.

It is not the purpose of this note to discuss the merit or demerit of sympathectomy, its paradoxical therapeutic effects or the unwanted disturbances of vasodilatory innervation. Vasodilator sympathetic nervous function has been well discussed in articles by Uvnäs,[2] Glover[3] and Roddie.[4] It is evident that the behavior of the sympathetic nervous system may be exploited in therapy before resort is made to operation which will destroy some of its function forever.

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Cardiac resuscitation

There are only a few situations in medicine today in which the physician feels almost completely helpless. Sudden and unexpected cessation of cardiac activity is one of these. When it occurs in the physician's presence during a house call or in the office there is great desire to "do something." Intracardiac injections of epinephrine, thumps on the precordium and artificial respiration are usually tried. The death certificate is soon filled out.

Unfortunately, sudden cardiac arrest does not always occur only in the elderly or the chronically ill. It may strike the relatively young adult who seemingly healthy. Dr. Claude Beck has pointed out that death can occur suddenly after a clean bill of health. He found that 63 per cent of the victims of coronary heart disease who died suddenly had no pathologic evidence of recent disease in coronary arteries or muscle.

Accidental and certainly reversible death is very common Electrocution drowning suffocation from many causes occur daily The body needs only an opportunity to regain its equilibrium of balanced metabolism and spontaneity for a normal life to continue

In the past decade it has become widely fashionable to open the chest and attempt resuscitation of the stilled heart by direct cardiac massage In the operating theater this is a well regulated and well executed maneuver of treatment of cardiac arrest On the medical wards and with extension outside of the hospital to the golf course and street it can become catastrophy The overzealous opening of chests by the house staff in almost all patients who die whether such a procedure is indicated or not has raised much criticism Stahlgren and Angelchik recently reported the results of attempted resuscitation of 25 patients outside of the operating room Only one patient recovered completely Five patients had evidence of brain damage during temporary survival of from 1 hour to 5 days

Stephenson[3] has stated that the most common cause of failure in cases of resuscitation of cardiac arrest is the delay in institution of cardiac massage This is due not only to lack of equipment but absence of personnel mentally ready to open the chest There has been no problem in providing ventilation of the lungs since expired air ventilation can be given readily by the mouth-to-mouth technique

Closed-chest cardiac massage provides a simple and clinically proved method of immediate artificial circulation It is the rhythmic intermittent forceful compression of the lower sternum toward the vertebral column The heart between is massaged When used together with artificial respiration oxygenated blood perfuses the body Time becomes available with this artifical oxygenation system for administration of cardiotonic drugs or defibrillation as are necessary

The physician need no longer have the despair of inability to meet the challenge of sudden unexpected cardiac arrest He can do something that has a good chance of returning the patient at least to his pre-arrest cardiac and central nervous-system status

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Pulmonary, aortic and precordial rheography in heart insufficiency and in patients with pulmonary arterial hypertension

For the study of contractile function of the myocardium of the right and of the left ventricles separately, the author proposed and elaborated the methods of pulmonary and aortic rheography

The method of rheography was proposed by Holzer Polzer and Marko in 1945 This method is based on registration of the changes in electrical resistance of living tissue to electrical current of sound frequency In the Soviet Union the method was studied by A A Kedrov with T L Liberman and A I Naumenko and Z A Levina with collaborators According to their data the rheocardiogram obtained by placing electrodes in the manner used for Lead II of the electrocardiogram reflects the changes in blood supply in the great arterial and venous vessels In recent time the Austrian authors Polzer Heeger and Schuhfried have elaborated the method of chest rheocardiography (wherein one electrode is put on the right shoulder and the other on the region of the heart beat) However the determination of absolute values for duration of the separate phases of the cardiac cycle by analysis of chest rheograms and electroplethysmograms of the trunk meets with some difficulties Independently of Heeger we elaborated a method of precordial rheocardiography reflecting mainly changes in blood supply of the heart ventricles by putting electrodes over the region of the heart beat and on the third left intercostal space at the sternal edge The phases of cardiac activity can be distinctly determined on the precordial rheogram However detailed analysis of dissociation in the work of the right and left ventricles in pathologic states on the precordial rheocardiogram is often difficult For registration of aortic rheograms two variants of electrode application were used In the first variant, one electrode was put on the second intercostal space to the right of the sternum and the second in the region of the aortic arch In the second variant one of the elec-

trodes was pplied in the region of the ortic arch and the econd over the bdominal aort For regi tration of lung rheogram one of the electrodes is applied on the second left intercostal space to the left of the sternum and the second over the thora on the third intercostal space on the nterior axillary line

Rheograms w re recorded w th the rheograph which w constructed in the Inst t te of Therapy f the Academy of Medical Sciences Moscow by on engineer Gugum sound frequency rrent of 70 kilocycles w used The rheogr ph electrodes were connected with the first ha nel of the electrocardiograph the ure of electrodes sed for recording was 6-7 cm According t our dat in healthy persons the begin g of sy tolic les t in the lung rheogram precedes by 0 01 0 03 second appears imultaneou l with or begin l ter than the beginning of the systolic ncrease in the ortic rheogram (the first arra t of electrode po tion) The results obtained giv upport to the suppo tion that lung nd aortic rheograms reflect blood upply of lung art ry nd aorta

We est bli hed the following changes in the lung rheogram which characterize the increase in blood pres ure in the pulmonary circ lation (by or pulmonale) (1) The summit of the lung rheogram is significa tly lat and occurs either t the beginning or t the time of the second sound (2) The lung rheogram is ignificantly smooth beca se of the plateau disappearance nd secondary w es (3) The scending branch of the lung rheogram ppears more tha 0 03 second later tha the scending branch of the aortic rheogram (4) The nterval from the Q w of the electrocardiogram t the ascending branch of the l ng rheogram is more tha 0 15 second

I patient with mitral heart disease w thout significantly marked *pulmo nary sclerosis the eleva* tion of blood pres ure in the pulmonary circulation was accompanied by significa t (more than 0 15 second) lengthening of the t me ter l from the Q w of the electrocardiogram t the scending branch of the lung rheogram in thi ca e the summit occurs before the second sound

The decrea e blood pres ure in the pulmonary circulation (medical treatment with reserpine nd E phyllin in cor pulmonale commissurotomy in patient with mitral stenosis) is accompanied by normalization of the lung rheogram

I congestiv heart in fficiency in patient w th therosclerotic cardiosclerosis we found relativ shortening of the phase f rapid entricular filling determined on precord l rheograms

I energetic d namic insufficiency (for example in patient w th thyrotoxicosis hypokalemia et) we found marked hortening of the ejection period (determined on aortic pulmonary and precordial rheocardiograms) and a significant lengthening of the electrocardiographic systole in th case the end of mechanical systole preceded the end of the T w of the electrocardiogram by more than 0 03 second which never ob erved in cases of congestive heart failure

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Experience with transseptal left heart catheterization

The development of ariety of techniques of left heart catheterization is indicativ of the variety of purposes for which acces to the left heart chambers may be needed I nstances of alvular heart disease it is usually desirable to record pressures from both left trium and left entricle and to deliver either an indicator or radiocontrast material int either chamber I review 1959 Bjork and Lodin[1] concluded that either transbronchial or para ertebral needle puncture of the left trium was suitable for catheterizing both chambers in ingle procedure Since that time transseptal left heart catheterization ha been introduced This report will present briefly our experience w th Ross technique of transseptal catheterization w th re gard t incidence of successf l studies and to mor bidity

A group of 81 patients has been studied all except one were adults The technique of trans septal catheterization has bee reported in detail elsewhere[2] nd will not be repeated here Our only modifications ha bee t increase the size of the Ross needle t 16 gauge and recently t 1 gauge in order to permit the passage f larger inner catheters to the left entricle W emphasize the desira bil ty of ing the right saphenou ein since in both instances in which the left saphenous ein was used the procedure as nsucces ful On several occasions the po tion of the t p of the needle in the left trium was such that initial attempt to pa the inner polyethylene catheter across the mitral al were unsucce ful thi was usually corrected by repeating the puncture in different position on the interatrial septum On t occasions an overhand knot formed on the inner catheter in the left atrium These were uneventf ll removed through the septum by completely withdra ing the needle and both catheters as unit

The number of times in which the various cardiac chambers were successfully entered was as follows. Of 81 attempts the right atrium was entered in 80 (99 per cent), the left atrium in 76 (94 per cent), and the left ventricle in 65 (80 per cent). Failure to reach the right atrium occurred in one patient with small tortuous veins of the right iliac vein at the level of the sacrum. Of the four other instances of failure to reach the left atrium, one attempt was from the left saphenous vein only in a child, and two patients presented unusual anatomic conditions of the left atrium. Both of these had undergone previous cardiac operations, and at subsequent autopsy were found to have massive old mural thrombi in the left atrium. These thrombi seemed to account for the fact that despite repeated thrusts in the appropriate area of the septum the tip of the needle could not be positioned in the left atrial cavity. Of the 76 patients in whom the needle was positioned in the left atrium, there were 11 (15 per cent) in whom the inner polyethylene catheter could not be advanced into the ventricle. In all of these, mitral valvular disease was thought to be present, usually mitral regurgitation.

In comparison with our previous experience with the paravertebral technique, these patients were more comfortable in the supine position, so that pulse rates were usually normal during the procedure. On several occasions there was transient mild pain in the neck and shoulder at the time of needle thrust. This usually indicated an unsatisfactory position and was not seen when the needle was placed in a correct position on the septum.

Postoperative morbidity has consisted of one wound infection at the saphenous cut-down site, one transient mild right facial weakness, and one case of superficial thrombophlebitis on the side of the cut-down. There have been no serious sequelae and no known pulmonary emboli related to the procedure.

The over-all rate of success in obtaining the desired measurements in this group of patients was not so high as the 96 per cent reported for the paravertebral technique by Hancock;[3] however, not all groups using the paravertebral method have obtained such good results, and some of the disadvantages of this method have been pointed out by Björk.[7] The 80 per cent rate of success with the transseptal technique here is the same as that reported by Ross and associates,[2] and the same reasons for the unsuccessful attempt have been encountered. One report of 71 per cent successful transseptal left ventricular catheterizations has dealt with a relatively small number of attempts.[4] Another group[5] has recently reported findings similar to ours. Mitral insufficiency is the main reason for inability to catheterize the left ventricle, and the use of a stiffer catheter may be an answer to this problem. Whether this will involve an added risk of dislodging left atrial thrombi will remain to be seen. Extra care must be given to the elimination of damping of the pressures which are being measured through the long inner catheter. The other disadvantages of this method are the slight additional time involved in isolating the saphenous vein and in blindly attempting to pass the polyethylene catheter across the mitral valve. There is also the improbability of obtaining selective left ventricular angiograms through a small inner catheter due to recoil. Modifications in technique have been suggested recently which may overcome all of these problems.

Several reports on the morbidity—frequently mild and occasionally serious—of the paravertebral technique have appeared. The negligible discomfort during the transseptal procedure in this group of patients and the infrequency of significant postcatheterization complications have been quite favorable by comparison. It is concluded that this technique represents a substantial improvement in terms of morbidity and risk in left heart catheterization, while permitting an incidence of satisfactory results which compares well with the other available methods. It is to be expected that modifications in the present technique will overcome some of the disadvantages mentioned.

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Book reviews

THE SURGERY OF MITRAL STENOSIS. By Robert P. Glover, M.D., M.S. (Surg.), F.A.C.S., F.A.C.C., Director of Surgery and Chief of the Thoracic and Cardiovascular Surgical Service, Presbyterian Hospital; Chief Thoracic Surgical Services, Episcopal, Fitzgerald Mercy, and St. Christopher's Hospitals; Assistant Clinical Professor of Surgery, University of Pennsylvania School of Medicine; Director, Glover Clinic, Philadelphia, Pa.; and John C. Davila, M.D., F.A.C.S., F.A.C.C., Research Director, Cardiovascular Research Laboratory, and Associate Thoracic Surgeon, Presbyterian Hospital; Associate Thoracic Surgeon, Episcopal, Fitzgerald Mercy, and St. Christopher Hospitals; Instructor in Surgery, University of Pennsylvania School of Medicine; Research Director, Glover Clinic, Philadelphia, Pa. New York, 1961, Grune & Stratton, Inc. 219 pages. Price $9.50.

This monograph is essentially a summary of the authors' considerable personal experience with the surgical treatment of mitral stenosis. The sections on the anatomy and pathology of the mitral valve and the techniques of mitral commissurotomy are particularly good, and it is in these fields that the authors have made notable contributions. The sections on the selection of patients, postoperative management, and results parallel the writings of other investigators in this field. The authors present their personal opinions on several areas of mitral surgery which are currently controversial, such as left-sided versus right-sided approach, frequency and techniques of mechanical dilatation of the valve, and indication for open-heart surgery in mitral valvular disease. The book is exceptionally well illustrated, and an appendix is included which presents in detail long-term results. Perhaps the chief value of this book is that it combines in concise form a large volume of material which is scattered throughout the world literature on the surgical aspects of mitral stenosis.

ADVANCES IN INTERNAL MEDICINE. Edited by William Dock, M.D., State University of New York College of Medicine at New York City, and I. Snapper, M.D., Beth El Hospital, Brooklyn, N. Y. Tenth edition. Chicago, 1960, The Year Book Publishers, Inc. 390 pages, 14 tables, 19 figures, 43 plates. Price $10.50.

There are 10 sections in this volume. Only those dealing with topics which are within the scope of the *American Heart Journal* are reviewed here.

Surgical Treatment of Mitral Stenosis and Aortic Stenosis by Charles Baker Guy, Hospital, London. History of mitral valvotomy from the nineteen twenties is reviewed briefly with discussion on immediate and late results of the operation. Follow-up studies on 239 consecutive patients who underwent the operation are reported. Deterioration after valvotomy in the presence of eight complicating disorders is cited and the prognosis in these cases indicated.

With improved techniques including open-heart surgery, relief of mitral stenosis is more accurately accomplished and with fewer undesirable sequelae.

Successful surgical treatment of mitral and pulmonary stenosis has led to the more exacting problem of surgical relief of aortic stenosis. Etiology, incidence, signs and symptoms of severe aortic stenosis along with difficulties involved in surgical intervention and results of surgery are discussed.

Newer Diagnostic Techniques in Congenital Heart Disease by Eugene Braunwald and Andrew G. Morrow, National Heart Institute, Bethesda, Md. The importance of determining precisely the anatomy of congenital heart lesions and assessing their detrimental effects on circulation in considering the desirability of an operation and its type and timing justifies this summarization. The diagnostic procedures are right and left heart catheterization, blood oxygen analyses, foreign gas techniques, indicator-dilution techniques, angiocardiography, phonocardiography, and electrocardiography.

Indications for and Results of Surgical Treatment of Congenital Heart Disease by Maurice Campbell, Guy's Hospital, London. Persistent ductus arteriosus, atrial septal defect, ventricular septal defect, pulmonary stenosis, coarctation of the aorta of the acyanotic group, and tetralogy of Fallot of the cyanotic type of congenital heart diseases are discussed from the viewpoint of indications for operation, operative mortality, and results. The purpose of complete cure has been attained for persistent ductus arteriosus only. Even though other types of congenital cardiac conditions can be improved now, the author anticipates the lapse of many years before their cures can be effected.

Clinical Phonocardiography: Graphic Analysis of Clinical Auscultation by Arthur Grishman, Sel y B Blefer and Ephraim Donoso, Mount Sinai Hospital, New York City. The importance of phonocardiography is stressed both as a teaching tool and a clinical aid. Newer and more accurate methods of recording are briefly outlined. The mechanism of production and characteristics of normal heart sounds are described. Phonocardiographic features of eleven common cardiovascular disorders are discussed. The 16 plates of graphic recordings illustrate well the above-mentioned subjects under study. Intracardiac phonocardiography is mentioned as being still in the research stage with many technical difficulties to be worked out.

Diagnosis and Management of the Curable Forms of Hypertension by David Crob, State University of New York College of Medicine, New York City. The author states that approximately 20 per cent of patients with high blood pressure the cause of hypertension can be demonstrated. Unilateral or bilateral kidney disease, coarctation of the aorta, pheochromocytoma, Cushing's syndrome, primary aldosteronism and certain diseases involving the midbrain are listed ... primary

etiological factors These are considered under the heading of clinical manifestations mechanism of hypertension diagnosis and management Dr Grob has crowded large amount of ery useful information into this summarization of the subject

This olume is composed of a ery interesting aluable series of articles all of which ha ade quat or extensive lists of references

Advances in Biology of Skin Volume I Cutaneous Innervation (Proceedings of the Brown University Symposium on the Biology of Skin 1959) Edited by William Montagna Arnold Biological Laboratory Brown University Providence R I New York 1960 Pergamon Press Inc 303 pages Price $10

Brow University in Rhode I land sponsors a yearly symposium devoted to the biology of the skin The material presented t the symposium in 1959 now publ hed in the form of book The authors ha incorporated importa t part of the discus ions in their chapters in a formal way thus gaining uniformity of course w th some di regard to the informality The result is h however that t is hoped that even the material from f turn sympo ia ill be published in the same manner

Eight of the nine chapters are devoted to different pect of the somatic nervous system The cutaneous ner end-organs in different regions of the kin are described in detail nd much ttention is paid to the interesting question of whether the specialized end-organs are modified according t the function or according to the region in hich they are found Arguments for the latter po nt of iew dominate H tochemical pect of skin inner tion are discussed in chapter entitled Cholinesterases in the Cutaneous Nerves of Man One chapter deals w th the possible correlat on between the sensory modalities such as pain heat and cold and the size of the fibers hich mediat them The central paths and the central projections of the afferent impulses from the skin are dealt with in one chapter and in another studies related to the mechanism of common sense are presented From the clinical point of iew tching is an important symptom The last tw chapters covering different aspects of pain and itching should therefore be of particular importance especially t the dermatologi t

Cutaneous structures know to be inner ated by autonomic nerves are blood essels swe t glands d pilomotor mu cles There has been much speculation hether there re both asodilator nd asocon trictor nerves in the skin Little need be said about the ex tence of asoconstri tor nerves but not much is known bout how the asodilator mechani m orks Vasodilatation could be brought b t by pecif sod lator nerves inh bition of asocon trictor tone or by liberatio of sodilator substances in sociation with activity of th swea gland These and other problems concerning autonomic innervation of cutaneous structures are discussed in chapter devoted t the autonomic innervation of the skin.

This book should be of great alue to the dermatologist as well to the experimental investigator

Laennec His Life and Times By Roger Kervran (tran lated from the French by D C Abrahams Curnel) New York 1960 Pergamon Press Inc 213 pages Price $3 50

One of the most interesting medical biographies that I ha e read for long time this book about the life and times of remarkable figure in French medi ine t the turn of the century 150 years ago I reading of Laennec s boyhood trial and tribulations at the time of the French Revolution of the difficult restoration of the monarch after the fall of Napoleon of his truggles with the un ympathetic Parisian medical profes ion (perhaps because he was strictly an out ider from Brittan) and of his ill health from the time he as a youngster one can think his luck stars that he did not li at this time in history diffi cult as the stress and strain of modern orld events may seem Tuberculosis was a great problem of health in his day nd his own family was apparently riddled by t although his father as still ali t 80 t the time of Laennec s ow death undoubtedly from tuberculosi t the age of 45

Laennec as born in 1781 in Quimper Brittany nd his uncle the Rector Michel Laennec baptized him A brother was born the next ear and three years after th t sister A year later his mother died doubtless of t berculosi t the age of 32 His father ho seemed t ha been ery robust a Councillor w th stormy political hi tory as unfortunately unstable character and it his uncle Dr Guillaume Laennec ad Guillaume son also largely supported and sponsored Rene Theofile H acinth Laennec nd steered him into his professional career Théofile as follower and pupil of Corvisart and at one time supporter of Napoleon himself

I 1795 t the age of 14 he ked an orderly in the Hotel Dieu in Nantes his ncle t that time being chief surgeon to the Army on the Brest coast Brittan Later he as placed under his ncle at the Hopital d la Paix dressing and t eating wound and becoming accustomed to minor urgery H stud ed anatomy and d section t the Hotel Dieu during this time Thus in his teens he began his initiation into the field that absorbed him for the next thirty years until h death E en at that early age he as in ncertain health which he neglected constantly orking ery hard

I 1 97 at the age of 16 he thought of embarking as surgeon on one of the corsairs going out from Nantes but his young stepmother d uaded him from this project and also tried to

steer him aw y from medicine which she c lled profes ion for fool compared with money which could be made by honest trade In 1797 a young cou Méri adec was born a ery im port t incident in Théofile life because of the fact that this young ousin who l ter went i to medicine him elf nherited Théof l s large prac tice when be retired n the eighteen t entu having worked w th h m for some years in Paris Al in 1797 Théofile resumed his duties i the military hospitals and his ourses at the Hotel Dieu in Nante He w appoi ted sur eon in 1799 Lat 1799 N poleon seized power after driv ng out the Directoire

F nally in the spring of 1801 Théofile at the age of 20 years arrived in P ri t enter more serious medical training n the pital I those early day of the nineteenth century Théofile was much interested medical history nd wrote thesis for entrance to the l rn med l fraternity on H ppocrates nd his teach ngs He lso prepared an extensive tre tise on pathology consist ng of 800 pages which was never pub li hed however in l rge part because of h quarrel w th Dupuytren It a labor of los and was tilized later his book on uscult tion and pulmon ry dise se publi hed 1819 During this period he was recei ed by Pope Pius VII in 1804 and ncidentall bec me enthusiastic member of the Celtic Academy in 1805 On his holiday that yea he studied the language of hi home cou try Britta y and was partic larly interested n the music and poetry of this Celtic tongue

From 1806 on ard he developed ery busy practice in Paris nd ontinued his writ ngs nd editing fact he became editor of the *Journal de Medicine* He loathed doctrines and system including that of Brown which was so popular that day but he w mportant follower of Corvisart and in 1808 wrote a review of Corvisart *Treatise on Auenbrugger*

In 1810 hi brother died of tuberculosis t the early ge of 28 fter this brother had been in ol ed for 18 months in l tigation w th their spendthrift father That same year Théofile wrote memorandum on ang na pectoris which although currently of terest at that time w not well nderstood He was appointed doctor to Cardinal Fesch uncle of Napoleon who then was n his heyday H was also the priv te physicia to Monsieur nd Madame Chateau briand This was a great honor but a costly one involv ng him in the upkeep of carriage nd obliging him t buy elaborat clothes For some years he continued his busy practice and teaching which included his cl nical ting t the Salpêtrière Occasionally he would return for acations to Britt y especially t his famil estat t Kerlouarnec which was the scene of his final retirement and death some years later

I 1816 he beg his research on the stetho-scope and gave many demonstration of t use prior to the publication of his famou work on *Mediate Auscultation* which saw the light of d y in 1819 He had experimented w th many different kinds of wood i the prep ration of the stethoscope nd finally settled on a cylinder of light beech wood about a foot long pierced throu h the center nd composed of two adjustable part cupped at their extrem ties This he called the *stethoscope* It was also known medical trumpet This tre tise of his wa one of the clearest medical works published i France in that period of medical history and because of it he became widely known The book w s trans lated into English by Forbes nd he began to recei e many foreign student

Meanwhile his health was very bad and be cause of it nd h l ve for Brittany he left P ris in October 1819 to become rural landlord with much prestige t his f mily est te How ever because of his restless ne and desire t return to medicine he went back t years later t Pari where 1822 he wa ppoi ted full professor w s elected to the Academy of Med cine in 1823 and became officer the Légion d Honneur 18 4 Despite the honors th t he was now recei ng his health f led and t was evide t that he would not be ble to continue his practice A consult tion in Bordeau in the utumn of 1824 contributed exh ustion to his f tigued st te nd he soon retired per manently t Britt y for the short rem ining part of his lif after add tional strains due t his conflict w th Broussais powerful medical figure of the d y in Paris A marriage of con en ience occurred in December 1824 and th though lasting only to his death less than tw years later perhaps the h ppiest time h l fe

He labored in the preparation of new econd edition of his treatise which w publ hed in 1826 t about the time of his final illness and death from his pulmon ry disease Brittany on Aug 13 1826

It is evident that Théofile Laennec as an intelligent honest nd ndustrious physici de oted t medical cience but ery much of individualist H had host of devoted patient who were sorry t ha him lea P ris They were nherited by h cousi Mériadec It was unfort nate that Théof le was so seriou ly beset by famil troubles by his sickne nd by hostile rival but he was highly respected h ow cou tryside his f neral was ttended by pea t nd leading c tizen alike One of his great ources of relaxation was his nterest in philology H learned and wrote the native Breton tongue

This skill lly translated book w evidently written by ma who had t his dispo tion an enormous amount of material with great ac curacy in ts deta l It rem nd me of Cush ng *Lif of Osler*

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Editorial

The position of fundamental age studies

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The concern of scientists—as against mystics, quacks, and therapeutic optimists—with the control of human age processes, if we date it to Metchnikoff and Claude Bernard, is less than a hundred years old; the engagement of science in studying it as an immediately realizable project is less than ten. Gerontology in its modern sense dates from about 1950.

In these ten years its advocates have generated a large body of printed matter, set up many institutes, and held many conferences, from which, so far as the fundamental understanding and control of age processes are concerned, virtually nothing hard emerges which could be put honestly to a lay committee as evidence of definite progress. The view of some sources of research money that gerontology has now deservedly talked itself out of work is therefore comprehensible, but this ignores the time which is required in any pioneer project to be spent in cutting brushwood and reclaiming ground before a crop of fundamental experiments can be sown, let alone harvested. Though some of the time and effort spent so far has been wasted, a certain amount has been achieved in defining the problem, clearing old errors, raising a generation which knows the possibilities and difficulties of age research, and discharging various ill-judged or superficial ideas which would have had to be voided at some point. Accordingly, although it has borne no fruit yet in medicine, the work done may later prove more important than it now appears to be.

The root questions which determine the form of the age problem remain much as they were in 1950. In man and other warm-blooded vertebrates, vigor declines and disease susceptibility multiplies with increasing age. The rate of this increase under the best conditions has a characteristic value in each species, and is exponential, so that there is a maximum practicable life span which further betterment does not lengthen.

Mammals are made up of three biologic components: cells multiplying clonally throughout life (white corpuscles, epithelial cells), cells incapable of division and renewal (neurons), and noncellular material which may have much or little turnover (collagen, intercellular substance). There are accordingly three grand classic hypotheses of the mechanism of senescence (not necessarily mutually exclusive) which must at some stage be dealt with—that vigor declines through change (epigenetic, mutational, infective, immunological) in the properties of multiplying cells; that it declines through loss of, or injury

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nonmultiplying cells and that it declines through primary changes in the inert materials of the body. All these are old hypotheses dating from Francis Bacon; none has yet been investigated by convincing experiment. At present interest in mutation and in matters such as somatic aneuploidy has focused attention on the first hypothesis—that new cells in old animals are not so good as new cells in young animals. Szilard's recent speculations[11,12] fit better to the second hypothesis—that irreplaceable cells are lost with time. The third hypothesis has generated extensive and important work on collagen and related substances—this is probably the only branch of gerontology widely known to physicians; for that reason it will not be summarized here.

One preliminary of any choice between these possibilities has been the need to observe the aging and age mortality relationship of animals other than men and rodents (which until recently were the only mammals for which we had life tables) and the study of factors which appear to hasten or delay the decline of vigor. This has been begun though slowly. Another requirement is the detailed study of cell populations and numbers at different points in the life cycle; a third is the comparison of the new cells of old animals with those of young animals. None of these has yet been adequately attacked. The decline of brain cell population at various ages in man[19,20] guinea pig[4] rat and even the honey bee[illegible] and termite[illegible] has been very variously estimated, whereas histochemical studies of old and young animals still frequently fail to distinguish between young cells in an old organism and cells which are themselves old—or between animals such as rotifers, nematodes and insect imagos in which there is no cell division or little and mammals in which fixed and endlessly dividing cells exist together.

Throughout its history the study of aging has been ruinously obscured by theory, and particularly theory *of a type which* begets no experimental hypotheses. The discussion of methods which has taken place and which has been quantitatively the main activity of gerontology so far has been worth while in laying some of these ghosts, and though it is depressing to see them being raised again from time to time by the darkeners of scientific counsel,[17] the most important recent contributions to theory, such as Szilard's stochastic and Burnet's immunologic speculations, all carry direct experimental consequences. It is noticeable that most of these theories have come from experimenters of international stature who are themselves working in other fields; serious progress in experimentation on age processes is really now waiting for some experimenter of equal caliber to devote his whole time to it.

It will be necessary here to discuss three theories, all of which have been contributed in this way—leaving aside the contribution of information theory, which at present records only established actuarial theory, though in a form which may prove instructive in the end. Thus, though the difference in life span between species can be treated as a difference in initial information content,[13,14] we are no nearer translating this into material terms. Even though none of these seems likely in itself to explain aging, they merit close attention as evidence of the way in which aging research and control have come to present themselves in practical terms to scientists of high ability, and it is this fact, rather than the theories themselves, which makes it possible that fundamental progress in the understanding of the loss of vigor with aging may be closer than the standard of experimental papers might lead us to think. Of course understanding and control are very different things, and the medical relevance of understanding the age process will depend upon what we understand it to be.

Vertebrate vital statistics

Some choice between hypotheses of aging might be made by comparing the shape of the age mortality function with other characters of the life cycle, but not so long as man and rodents were the only available source of vertebrate vital statistics. Some of the difficulties of getting this kind of information in sufficient quantity and quality have been described elsewhere;[11,1] figures have eventually been forthcoming for dogs[14] and horses[15] and

for small series of ruminants in zoos from existing records and a lifetime study of beagles is now being undertaken[14] as a by product of radiation research where the interrelation of life span body size and cell number has become a critical issue in determining the percentage decrease in longevity per rem[24] There are still no proper figures for birds under protected conditions or for cold blooded vertebrates but a laboratory study of an experimental fish[1] population has failed to support Bidder conjecture that animals of indeterminate growth should not age the age dependent mortality of a small fish (Lebistes) behaves almost exactly like that of a rodent It remains to be established how far the much longer lives of fish and reptiles compared with mammals of similar size are the result of longer sustained or more extensive cell replacement they might imply lower vulnerability to copying faults at lower chromosome numbers

Fresh theoretical attempts have been made to relate the time scale of aging to other factors such as size—the closest correlate seems to be the index of cephalization i e the excess of relative brain weight over the average for all mammals This relationship holds good both between species—though admittedly upon inadequately characterized data for life span — and in dogs between big and small breeds within a species but the significance of it is obscure

Factors modifying the age dependent increase in mortality

Underfeeding McCay s original observation[19 21] that rats can be made to live twice as long as usual by severe but controlled underfeeding remains a key finding which has been little if at all elucidated in thirty years It is still not clear whether continued growth postponement of differentiation or a specific damage effect of high intake of food is responsible

The literature of life prolongation by underfeeding has been recently reviewed[18] in a great many animals from suctorians[41] and cockroaches to rodents the optimal intake of food for growth is not the optimal for longevity In rats and mice at least two effects seem to be present—a reduction of disease with sparer diet and an actual postponement of development including senescence the effects of mild restriction probably represent the first and of severe restriction the second Rats which receive a diet adequate in all but calories can be kept immature and strikingly free of the diseases which affect full fed litter mates After restriction in this way for periods up to 1 000 days the survivors were able to resume growth mature sexually and live in all substantially longer than controls The gain in further expectation was not equal to the period of restriction and was greater in males than in females The retarded rats were active but immature[1 19] in early experiments the main finding was that members of each retarded group were still alive after all controls had died and the gain in life span was limited to the survivors of a substantial early mortality but the aggregate curves based on later experiments[1] show definite lengthening of the adult plateau and displacement of the modal age of death

In Wistar rats the gain in life is roughly proportional to the severity of the under feeding—starvation for one day in three or four produced a significant increase in mean life [8] The gain was greater on an omnivorous than a vegetarian diet [7] By a fast of one day in three the mean expectation can be increased by 20 per cent in males and 15 per cent in females without arrest of growth [6]

Experiments in mice have given very similar results Both total and reproductive life are increased by restriction of calories On a diet which continued half the calories (as lard and dextrose) in the standard diet C3H females which are normally sterile at 11 12 months were still breeding at 21 months A fast of two days out of seven with or without the addition of nucleic acid to the diet produced an increase of 50 to 60 per cent in the life of albinos[33] There is also a large literature of the special effects of limiting particular dietary ingredients in particular strains [47]

It is still not possible to relate these observations clearly to the causation of aging in rodents The operative effect of underfeeding seems to be a dietary hypophysectomy [42] The apparent youth of underfed rats extends to the contractility

of their tail collagen which remains young in pattern[9] it has been claimed that their cells have a shorter latent period in tissue culture than that of controls[31] Dietary size limitation depends upon a smaller cell number retarded animals have the cell population appropriate to size group not age group At the same time their irreplaceable cells may be protected as judged from the reduction in degenerative disease though basal metabolism is significantly higher than in unrestricted age mates[32] Fundamental research is badly needed to interpret these observations in terms of aging theory

Radiation It is not yet clear whether the involvement of age studies with radiation biology will prove to be the key to the nature of aging or a mischievous diversion of energy—it has at least focused on age processes the attention of workers who would not have examined them otherwise and has induced them to set up long term studies Exposure to ionizing radiation shortens life It differs from the many other agents which do this in the close resemblance between its effects and the natural loss of vigor due to aging which it appears to accelerate In exposed rodents a single exposure in early life produces a loss of expectation equivalent to a jump forward in age the slope of the decline in the exposed population running parallel to but earlier than that in controls in linear proportion to the dose life long exposure from birth produces a scalar contraction of the whole survival curve[33] The important question for age studies is whether this shortening represents an acceleration of the process or changes which normally induce loss of vigor whether it reduces vigor by some other unrelated changes or whether like noise or exposure to traffic risks it is simply an addition to the environmental attack rate If radiation hastens normal aging it should cause the failure of homeostasis to appear earlier in life without affecting its form and the exposed animals should die at younger ages than the controls but of the same diseases in the same sequence In the biggest and most recent study of one shot irradiation applied to mice Lindop and Rotblat[3 4] carried out detailed postmortems on all the animals they found that although the survival curve is moved toward the origin in a way which indicates a decrement in vigor the order of diseases in irradiated and control animals is not identical and the action of radiation is therefore presumably not a simple moving forward of the normal age process

Theories

Germane to the interest of radiation biologists in aging and age biologists in radiation are three theoretical suggestions all unproved all open to various objections, but all intelligent and original enough to be regarded as significant The first is simply the idea that the predominant process in aging is somatic mutation leading to changes in the properties of clonally dividing cells and loss of capacity in fixed postmitotics Its cause would be the sum of mutagenic influences on the body and if radiation accelerated aging it would do so in part at least by increasing the mutation rate[35] The first suggestion of this in the literature seems to be that of Kunze[6] who put it down to cosmic rays In putting it forward again Failla points out that the large discrepancy between the observed and calculated background equivalent dose in irradiated mice can be removed if we allow for exposure to background in prenatal life when radiation sensitivity is substantially higher Failla is the originator of the term hit to describe a hypothetical lesion—point mutation chromosome loss or other—occurring in a cell and inactivating it The term has been taken further in the elaborate stochastic model devised by Szilard [9]

Szilard assumes that the elementary step in aging is a hit (not necessarily by a radiant particle) which renders inactive all the genes on one chromosome of a somatic cell Hits are random events the probability of any one chromosome being hit remains constant throughout life and the over all rate of occurrence of hits is characteristic of the species As a result of hits the proportion f of adequately functioning somatic cells declines with time until it reaches f^* at which point the probability of death within unit time (in man one year) is unity

At the same time each individual is assumed to carry a load of genetic faults

A fault is a mutation in one of the genes essential to the proper working of a somatic cell Szilard assumes that the number of these genes in man is 3 000 out of a probable total of 15 000 A cell becomes inoperative when both of the pair of any such genes are put out of action Accordingly when a chromosome receives a hit the cell will cease to function (a) if the homologous chromosome has already also received a hit or (b) if the homologous chromosome carries a fault at any point By assuming probable values for several quantities which no one accurately knows Szilard proceeds from this model to draw plausible approximations to quantities which are known such as the concordance between twin ages at death He also proposes not an experimental proof but at least one critical experiment—the reduction of life span of the progeny of irradiated mice could support or negate the model

The model itself has other interesting implications One is that if *m* the number of chromosome pairs differs between species the specific life shortening per rem will be greater for that in which *m* is the smaller and vary inversely as $\sqrt{m}$ Szilard also works out on the assumption of an average on n = 2 5 inherited faults per head for the human female the modal longevity of a genetically perfect female with no such faults it comes to 92 as against the present 80 years If n > 2 5 it would be more

Szilard s model is deeply ingenious but for the biologist as for the late Ernie Pyle the first word which comes to mind is But Such simplified mathematical models can bring light to a subject—as did Morgan s assumption of the simple linearity of the genes—or merely darken it further For the model to be relevant at all it seems essential that aging should be timed by a fault in replication following the loss of one allele in the cell This raises two grave objections pointed out at once by Maynard Smith[22] and met by Szilard only at the expense of new variables[40] The first is that if the fault hit hypothesis is right the life of homozygous and inbred animals should be longer than that of heterozygous and hybrid animals whereas the reverse is almost universally true The second is that the only reason for Szilard s assumption that a hit inactivates a whole chromosome appears to be the need to find a hittable object yielding the right order of magnitude to account for e g the difference between male and female longevity there being too many genes and too few cells to do so It is also difficult to relate the whole model to the dynamics of cell division in a system which contains fixed and multiplying cells where faults acquired by stem cells as the result of hits will be communicated to a varying cellular progeny If the critical fraction f^* represents simply surviving cell number in general it is difficult to credit either Failla s or Szilard s version of the cell loss hypothesis even if the effect of a hit is not necessarily the physical removal of the cell Failla[1] for example assumes that vitality (the reciprocal of mortality) is $\propto f$ the proportion of effective cells remaining so that

$$\frac{f_0}{f} = e^{\alpha t} = \text{spontaneous mutation rate}$$

α being the slope factor of the Gompertz equation and he points out that in this case the hitting process must damage rather than destroy the cell as otherwise only 5 8 per cent of the cells alive in man at age of 35 would survive in him at the age of 65 Szilard s theory seems to give an almost equally high rate of cell loss whereas both completely ignore the question of replacement If on the other hand f^* represents a fraction not of cell number but only of an unspecified stuff vitality the further equations do no more than restate actuarial observation in new terms To make them experimentally useful it would seem that aging must be timed by the loss of key postmitotics (possibly in a single organ) or by a process with the same mathematical shape There is finally the difficulty common to all mutational theories of aging that chemical mutagens do not seem to hasten it or mimic the life shortening effect of radiation

The third stochastic theory by contrast with the Szilard Failla model places the emphasis specifically on the dividing cell but on one particular clonal system Antibodies are now thought to be produced by lymphocytes and the acquired power of making a particular antibody appears to be transmitted by a lymphocyte to

progeny. A mechanism not fully understood determines that lymphocytes shall not normally respond to their proprietor's body constituents by forming antibodies against them. Burnet has suggested that if mutation in lymphocytes followed by selection determines the various reactive capacities which they show and if one possible mutation is the loss of this negative specificity to homologous antigens then the organism might be expected to face a steady increase in autoimmune reactions with the passage of time—reactions which might well be of precisely the polymorphic diffuse and variable type which characterizes the infirmities of loss of vigor in aging, whereas the statistical constancy of the mutation rate and/or the rate of occurrence of Szilardian "hits" would remain to provide the stability of the survival curve on which life assurance depend.

The revival of immunologic age theories is an unexpected return to Metchnikov,[13] who always predicted that the same cellular mechanism would prove to be morphogenetic in the embryo, defensive in the adult and destructive in the end. Burnet's suggestion is open to experiment and may possibly be confirmed or refuted reasonably quickly. Moreover if true it would mean that aging was likely to be much more accessible to medical interference than it is now prudent to expect. It is not incompatible with some aspects of the Szilard-Failla model—the effect of a hit in this case is not that it removes a cell from useful activity but that it puts a cell and its progeny into harmful activity. Burnet's general theory of clonal selection seems to imply that mutational instability in the lymphocyte system is used adaptively by the body and moreover that the harmful mutation with loss of negative specificity also confers protection on the mutant against being "selected out" by normal body mechanisms, *f** being now no longer a cell balance below which we are bankrupt but the fraction remaining after a lethal percentage of cells has become corrupted in this way. Burnet's theoretical argument persuasively urges that something of the sort ought to happen. What is now required is experimental evidence that it does so.

Conclusion

From what has been said the position of fundamental age research stated in less rarefied terms is this: in spite of the lack of an inspired experimental line (if we except McCay's thirty-year-old work on rat longevity which has still not been properly worked out in a manner which shows why underfeeding lengthens life) and in spite of the desultory character of the experimental and the speculative character of the theoretical papers which have appeared, we may well be within striking distance of a concise statement of the chief process in the loss of vigor due to aging in human beings. The main requirement for this is probably (unless we rely on luck) the full-time attention of one or more first-rate experimental talent. The minor requirement, which is certainly necessary though it may not prove sufficient, is a detailed knowledge of the age trend in cell population, cell capability, and somatic cell variation—preferably in man since the real motive of age studies is to control in human beings the changes due to aging. It has to be remembered that the medical target of the immediate clinical studies, e.g., on collagen or on vital capacity, and that of work on fundamental age biology are different. So are their probable consequences. Unless the single given pathologic change or process which we happen to select is a major timekeeping mechanism in man, successful clinical work on it will make more people die at ages distributed about the specific age. This is the general tendency of medicine. *The aim of the biologic studies is to move the specific age itself and the age distribution of all age-dependent causes of death with it.* The possibility of doing this must depend upon whether we find that the general loss of vigor has an identity which can be attacked experimentally apart from its contributing parts. If, for example, the only unity in aging processes is that they depend on age-dependent changes in the intensity of natural selection[14,15] acting on our ancestors, the decline in vigor is not fundamentally attackable and can only be dealt with piecemeal. Apart from the equally urgent need to study human development as a unity, there is no other immediate medical problem which so clearly illustrates

our need for a specific medical biology and for a biologic orientation in our medical teaching—without it clinical studies risk finding themselves taking their direction from a group of scientific ideas with which clinicians will themselves not normally be familiar

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Clinical communications

The ineffectiveness of an inotropic agent, mephentermine (Wyamine), in the treatment of congestive heart failure

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The ability of mephentermine sulfate (Wyamine), a synthetic sympathomimetic amine, to augment strikingly the contractility of both nonfailing and failing canine hearts has been well documented. This agent acts primarily to elevate the ventricular function curve and to improve the efficiency of the dilated failing heart; its effects on the systemic arterial bed are minimal.[1] The drug is apparently well absorbed from the gastrointestinal tract and it apparently shows little toxicity. In view of these properties it appeared to be an ideal agent for the treatment of clinical chronic congestive heart failure.

Four patients with chronic inactive rheumatic heart disease (three with mitral and one with aortic regurgitation), one patient with arteriosclerotic heart disease, and one with myocardial failure of unknown etiology were studied. All patients had required a low salt diet, digitalis, and diuretics prior to hospitalization. The patients were studied in the hospital with daily observations of (1) their clinical status in regard to signs and symptoms of congestive heart failure, (2) body weight, and (3) sodium balance. Venous pressure was determined at frequent intervals. When congestive heart failure was present, as evidenced by increasing dyspnea, orthopnea, gain in weight, and a positive balance of sodium, oral Wyamine was administered in doses ranging from 25 to 500 mg. daily in divided doses. One patient received up to 200 mg. of Wyamine daily intramuscularly.

In no instance did the administration of the Wyamine appear to exert any beneficial effect on the congestive failure state. Two patients appeared to show slight worsening. Typical experiments are illustrated in Figs. 1 and 2. Two of the patients exhibited no side effects from the Wyamine, whereas the others showed nervousness and one patient had a transient psychosis.

The positive inotropic action of Wyamine demonstrated in the experimental laboratory appeared to exceed that exerted by digitalis glycosides. Therefore, the lack of clinical benefit resulting from the administration of the sympathomimetic amine was unexpected. It is possible that an effective dose level was not achieved and that had higher doses been employed, clinical benefit would have been apparent. However, this

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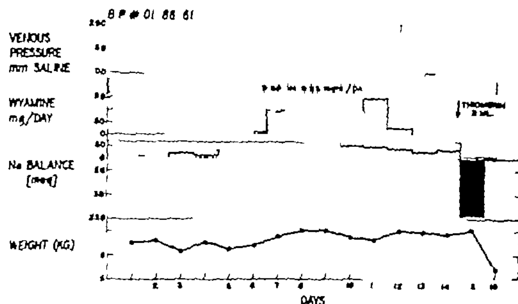


Fig. 1. Observations on the effect of Wyamine in a patient with rheumatic heart disease with mitral valve involvement and congestive circulatory failure. The intake of sodium was held constant at 60 mEq daily until the fifteenth day on which it was lowered. The patient had moderate dyspnea and no change in his congestive failure but during the administration of Wyamine the diuresis was induced with Thiomerin.

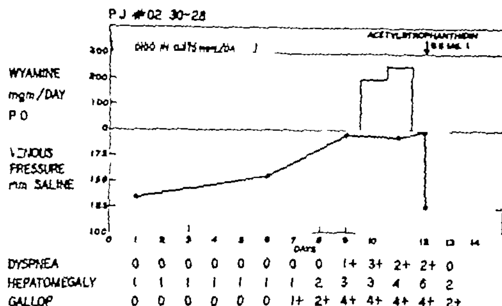


Fig. 2. In this patient with rheumatic mitral regurgitation the symptoms and signs of heart failure appeared several days after digitoxin was discontinued. Failure progressed while Wyamine was administered but promptly disappeared when he was given 0.8 mg. of acetyl strophanthidin. The severity of dyspnea and intensity of the gallop sound are graded on a scale from 0 to 4+ and the size of the liver is expressed in centimeters below the costal margin.

is unlikely since in two patients the heart failure actually became worse while they were receiving Wyamine. These observations emphasize that the state of clinical congestive heart failure is far more complex than the simple depression of myocardial contractility which may be induced acutely in the experimental laboratory and which responds readily to treatment with sympathomimetic amines and they would also

seem to underscore the clinical importance of treating the extracardiac manifestations of heart failure

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A preliminary study of the electrocardiogram of the normal premature infant

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With recent advances in the diagnostic methods and surgical therapy for cardiac disease, cardiologists are now asked to evaluate younger and younger patients, even in the premature infant age group. We soon came to realize that normal values have not been established for the electrocardiographic deflections and intervals of the premature infant. This preliminary study was designed to determine the range of normal of the several components of the electrocardiogram of the normal premature infant in order to enable differentiation of the pathologic from the normal electrocardiographic record.

Material

A birth weight of less than 1,500 grams was considered to be evidence of significant prematurity and was the criterion used for the admission of an infant to the study group. The seven infants studied were clinically well, with normal findings obtained on physical examinations at birth; the absence of cyanosis, cardiomegaly, congestive heart failure, and significant murmurs was specifically noted. A cardiac physical examination again confirmed the normal condition of the babies prior to their discharge from the hospital. X-ray examinations were not made. Follow-up physical examinations on a clinic basis were attempted after the infants were discharged from the hospital in an effort to confirm the normal cardiovascular status. The results are shown in Table I.

Serial electrocardiograms were taken on these 7 premature infants daily for the first week of life, three times during the second week, twice during the third week, and once a week thereafter until the infant had attained 2,000 grams, which is the requisite weight for discharge from the Grady Memorial Hospital Premature Nursery. In the infants studied, there was an essentially linear relationship between age and body weight. These seven infants varied from age 41 days to age 60 days at the time of discharge from the hospital. One hundred thirteen electrocardiographic records were thus obtained for analysis.

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Table I Follow up examinations

Patient	Age at last examination	Cardiovascular examination	Comment
1	11 mo	Normal	Well baby
2	4 mo	Normal	Moved out of Atlanta area
3	3 mo	Normal	Died suddenly t home 2 weeks after clinic sit—(aspiration)
4	13 mo	Normal	Recurrent upper respiratory infections
5	3 mo	Transient soft apical systolic murmur—otherwise normal	Lost to follow up
6	mo	Normal	Died suddenly t home 2 day after clinic sit—(a piration?)
7	10 mo	Normal	Recurrent pneumonia

Method

Electrocardiograms were recorded at the standard paper speed of 25 mm per second on the Sanborn Viso Cardiette The limb leads were recorded using standard extremity electrodes reduced in size to 2 × 3 cm Since suction electrodes were impractical in these tiny infants a standard electrode cut to 1 5 × 2 cm and mounted on a cork for insulation from the operator s hand was used to record Leads V V_2 V V_6 and V_{3R} in the positions recommended by the American Heart Association Alcohol sponges were used to reduce skin resistance During the recording of the electrocardiogram the infants were in the supine position with crying and kicking minimized by the use of a sugar nipple pacifier No sedation was administered at any time and indeed the initial tracing was taken at least 8 hours after birth to obviate the effects of analgesia and anesthesia administered to the mother during labor During the first week of life electrocardiograms were obtained by inserting the electrode wires and the operator s hands through the ports of the Isolette with oxygen and moisture being maintained as needed later recordings were done in an infant bassinet No attempt was made to establish any definite relationship of the recordings to feeding time of day temperature of the Isolette etc The body temperature of the infants varied from 93 to 100°F during the course of the study being partly influenced by the temperature of the Isolette

The data obtained from the electrocardiograms of these premature infants were compared with the data of Ziegler[1] for the full term infant of comparable age The values cited for the full term infant in all subsequent tables were reproduced from Ziegler s text with the kind permission of the author and publisher

Data

The average *heart rate* (Table II) of these premature infants gradually increased from birth to 9 weeks of age (140 per minute to 176 per minute) This was similarly seen but to a lesser extent in the full term infant whose peak heart rate was observed at 1 to 3 months Regular sinus rhythm was seen in all of our subjects with no sinus arrhythmia or ectopic beats noted in any record

The average *electrical axis of the P wave* for the entire age span studied was 40 degrees decreasing from a mean of 55 degrees at birth to a mean of 35 degrees at 9 weeks of age The P wave electrical axis seemed to parallel the QRS axis in the premature infant (Fig 1) whereas Ziegler found no relationship between the P wave and QRS electrical axes in the full term infant As Ziegler observed in the full term infant the greatest P wave amplitude was seen in Lead II However the absolute P wave amplitude was greater for the premature than for the full term infant in all leads In the premature infants studied the P wave amplitude was unrelated to age There was no correlation between the P wave duration (Fig 2) which remained relatively constant and the age or heart rate Greater P wave negativity was seen in Leads V and V_2 in the earlier weeks of

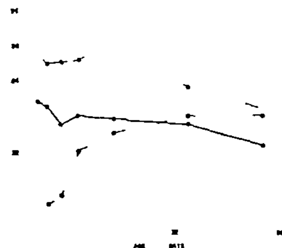


Fig. 1. Average P wave, QRS and T wave electrical axes in degrees.

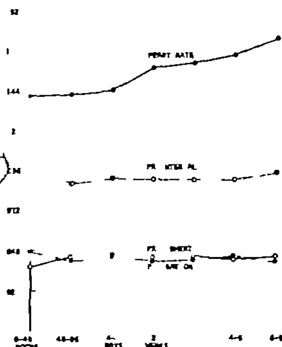


Fig. 2. Average heart rate, P-R interval, P-R segment and P wave duration according to age.

life in the premature infant than in the full term infant.

The *P-R interval* and *P-R segment* (Fig. 2) which varied but minimally, did not appear to be related to age or heart rate. The *QRS* and *Q-T intervals* (Table II, Fig. 3) seemed to diminish with increasing age and with increased heart rate; however, with the inaccurate method of measurement of the T wave, little significance can be attached to these observations. It was not possible to accurately differentiate U waves in any of these records.

The *electrical axis of the QRS* (Table III) in the premature infant averaged 75 degrees in the first 48 hours of life, with a range of −120 to +135 degrees. This represents a remarkably wider range of values than was seen in the full term infant. Of interest is the observation that for the individual premature infant there was relatively little variation in the QRS electrical axis in the serial records (Figs. 4 and 5). There was a slight decrease in right axis deviation with increasing age; the average QRS electrical axis changed from 75 degrees at birth to 50 degrees at the age of 9 weeks. This was similarly seen in the full term infant. Again of interest is the persistence of the wide range of the QRS electrical axis with increasing age in these premature infants (Fig. 6).

The *electrical axis of the T wave* (Table III, Fig. 1) shifted to the right as age increased, with a resultant diminution of the QRS-T angle. Conversely, the T wave electrical axis in Ziegler's full term infants tended to shift to the left with increasing age, paralleling the QRS electrical axis. To supplement these observations on

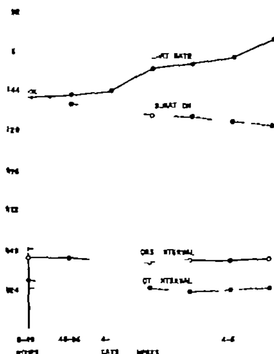


Fig. 3. Average heart rate, QRS interval, Q-T interval and T wave duration, according to age.

Table II *Average measurements for heart rate P R interval duration of the P wave P R segment QRS interval Q T interval duration of the T wave and Q T index at various ages*

Age	*Heart rate*	*P R interval*	*Duration of P*	*P R segment*	*QRS interval*	*Q T interval*	*Duration of T*	*Q T index*
				Full-term infant				
0-24 hr	125	099	051	048	065	294	143	4 1
1 day 1 wk	138	09	0485	0495	056	266	146	402
1 wk.-1 mo	16	09	048	047	055	238	117	385
1 3 mo	161	096	048	048	062	244	121	397
				Premature infant				
0-48 hr	140	101	047	038	043	288	143	439
48-96 hr	14	088	042	044	042	251	136	305
day 4 7	144	091	044	045	040	254	136	392
wk 2	155	091	042	044	040	245	130	398
wk 3	161	091	043	045	041	220	129	362
wk 4-6	166	091	045	043	041	23	126	392
wk 6-9	176	095	042	045	041	233	123	400

From R. F. Ziegler: Electrocardiographic Studies in Normal Infants and Children, 1951. Courtesy of Charles C Thomas, Publisher, Springfield, Ill.

Table III *QRS and T wave electrical axis (degrees)*

Age	*QRS axis*			*T axis*		
	Average	*Minimum*	*Maximum*	*Average*	*Minimum*	*Maximum*
			Full-term infant			
0-24 hr	137	75	190	77	−10	180
1 day-1 wk	128	75	190	34	−30	110
1 wk-1 mo	105	−5	180	41	−10	130
1 3 mo	6	35	135	46	0	90
			Premature infant			
0-48 hr	6	−120	135	19	−60	90
48-96 hr	77	−115	160	9	−30	45
day 4-7	73	−105	160	13	−60	65
wk 2	74	−170	160	33	−40	65
wk 3	80	−120	165	41	10	60
wk 4-6	62	−130	130	48	25	65
wk 6 9	52	−9	120	49	30	0
			50 additional premature infants studied			
0-48 hr	103	−80	155	30	−70	105

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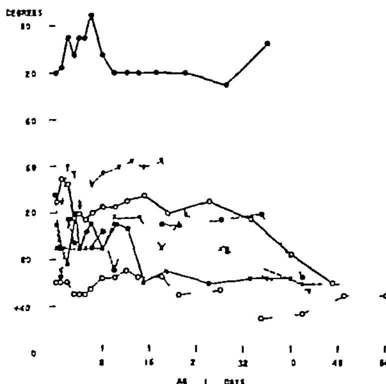


Fig 4 QRS electrical axis range for each premature infant studied

the QRS and T vectors an electrocardiogram was recorded on each of 50 additional premature infants during their first 48 hours of life analysis of the QRS and T vectors in these 50 premature infants further demonstrated a wider range of values than was seen in the full term infant (Table III)

The *magnitude of the QRS complex* as measured by the greatest QRS height in any precordial lead was unrelated to the age or the body weight of these premature infants

The greatest *incidence and amplitude of Q waves* (Table IV) was seen in Leads II III and aV_F both in the premature and in the full term infants However the electrocardiogram of the premature infant also showed significant Q waves in Lead aV_L. The Q waves in the electrocardiogram of the premature infant were of significantly lesser amplitude than those in the electrocardiogram of the full term infant The absolute incidence of Q waves was less in the premature than in the full term infant despite the fact that small Q waves were present in the electrocardiogram of the premature infant in a greater number of leads—i e there were fewer Q waves in the electrocardiogram of the premature infant but they were more widely distributed No Q waves were recorded in Leads V_{3R} V_1 or V_2 for the premature infant nor were Q waves reported by Ziegler in Leads V_1 or V for the full term infant There was a striking paucity of precordial Q waves recorded in the premature as compared with the full term infant The precordial Q waves when present in the premature infant increased in amplitude with lead progression from V to V_6 (as was the case with the full term infant) and we could demonstrate no significant change in Q wave amplitude or incidence with increasing age

The amplitude of the total *RS deflection* (Table V) both in the extremity and in the precordial leads of the electrocardiogram of the premature infant was considerably less than that reported by Ziegler for the full term infant In the limb leads of the electrocardiogram of the premature infant the *R wave* in Leads I and II became taller from birth to 9 weeks of age whereas R remained relatively unchanged this has been similarly observed in the full term infant The *S wave* in Lead I of the premature infant unlike that of the full term

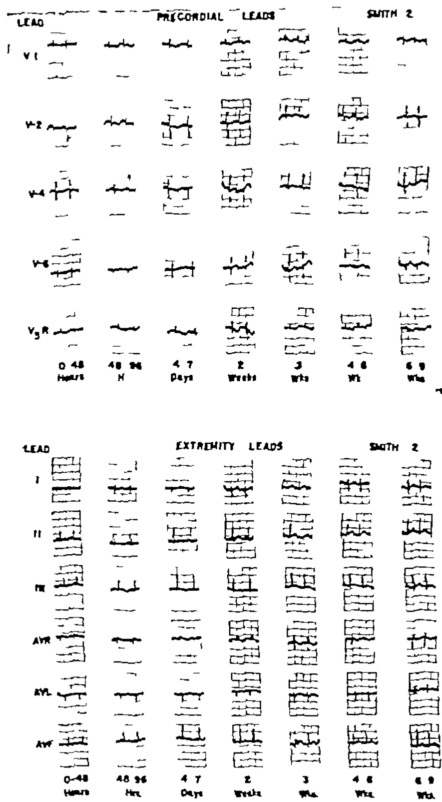


Fig. 3. Selected serial electrocardiograms on one of the premature infants studied (birth weight—1,160 grams).

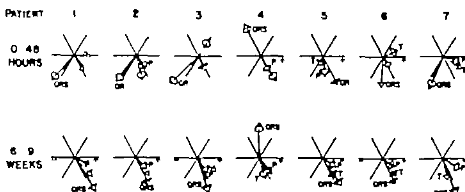


Fig. 6. Mean P, QRS, and T vectors for each of the 7 premature infants studied. The upper line diagrams the initial electrocardiogram of the series obtained during the first seven hours of life. The lower line diagrams the final electrocardiograms of the series taken when the infants attained a weight of 2,000 grams.

infant did not change significantly with age, the S wave in Lead III of the premature infant, however, became significantly smaller with advancing age, and this decrease in amplitude was far less pronounced in the full-term infant. In regard to the precordial leads, the R wave amplitude was greatest in the mid-precordial leads at all ages both in the premature and the full-term infant. In our records the R wave in Lead V was markedly greater than the R wave in Lead V (opposite to the observations in the full-term infant) with R_{V4} becoming increasingly prominent with age. The amplitude of all precordial R waves of the premature infant increased with maturity, with the change being least pronounced in R_{V1}; in contrast, the electrocardiogram of the full-term infant showed little increase in precordial R wave amplitude with age and R_V and R decreased considerably with maturity. Surprisingly, the precordial S wave showed no significant variation with age in the premature infant, whereas the records for the full-term infant demonstrated changes reciprocal with those of the R wave.

The incidence of *RST segment* displacement (Tables VI and VII), both elevation and depression, was exceedingly pronounced in the premature infant as compared with the full-term infant. This displacement averaged 1 to 2 mm. in the premature infant, both in the extremity and the precordial leads—a far greater amplitude than that seen for the full-term infant.

The *electrical axis of the T wave* (Table III, Fig. 1) shifted slightly to the right with increasing age (19 to 49 degrees from birth to 9 weeks of age), tending to approach the QRS axis as the QRS concomitantly shifted toward the T wave axis. In marked contrast to the frequently inverted T_1 and T_{AVL} of the full-term infant, the T_1 and T_{AVL} of the premature infants were usually upright in the first 24 hours of life and tended to remain so. In addition, the T_V of the premature infants was negative or diphasic until week 4 to 6, when it became constantly upright, contrasting with T_{V1} in the full-term infants, which was usually upright at birth and then became predominantly negative. T_{V6} was usually upright at all ages studied, both in the premature and the full-term infants. Precordial T negativity was commonly seen from T_V to T_V in these premature infants, as well as in the full-term infants.

Review of the literature

Interest in the characteristics of the electrocardiographic record of the premature infant was evidenced by sporadic reports in the literature as early as 1913.[3] Most authors[4] emphasized the evidence of right ventricular preponderance which was observed in the electrocardiograms of premature infants as compared with the records from adults, but varied widely in their delineation of the typical deflections and intervals of the premature infant record. Although minor differences were described between the electrocardiograms of the

premature and those of the full term infants it was generally agreed that there were no characteristics to specifically identify a record as that of a premature infant [4,28,1] however Thaon[19,7] and Angeli[13] believed that they could identify a specific premature pattern No relationship was noted between the birth weight of the premature infant and the electrocardiographic pattern [4,8]

Table IV Per cent incidence of Q waves at various ages

Age	*I*	*II*	*III*	V	V	V	V	V	V	V	V	V
					Full-term infant							
0-4 hr	3 14	7 0	100 0	72 0	6 28	87 5	0	0	0	7 4	60 0	73 5
1 day 1 wk.	21 5	93 0	96 5	32 0	10 7	93 0	2 cases	0	3 5	25 0	77 2	86 4
1 wk. 1 mo	22 5	87 5	93 0	55 0	5 0	87 5	0	0	9 1	41 6	87 5	93 0
1 3 mo	34 2	92 0	95 0	45 0	7 9	89 5	0	0	13 3	50 0	75 0	92 5
					Premature infant							
	I	*II*	*III*	V	V	V	V	V	V	V	V	V
0-48 hr	0	22 2	33 3	88 9	44 4	33 3	0	0	—	11 1	11 1	0
48-96 hr	14 3	78 6	28 6	78 6	42 9	28 6	0	0	—	0	21 4	0
day 4 7	9 5	33 3	33 3	76 2	42 9	23 8	0	0	—	0	19 1	0
wk 2	24 0	44 0	72 0	72 0	32 0	52 0	0	0	—	0	40 0	0
wk 3	13 3	40 0	60 0	80 0	0	26 7	0	0	—	0	13 3	0
wk. 4 6	21 4	42 9	64 3	64 3	35 7	50 0	0	0	—	7 15	4 9	0
wk. 6-9	6 6	73 3	80 0	60 0	20 0	73 3	0	0	—	13 3	53 3	0

From R. F. Ziegler Electrocardiographic Studies in Normal Infants and Children 1951 Courtesy of Charles C Thomas Publisher Springfield Ill.

Table V RS deflection amplitude in precordial leads (0 1 millivolts)

Age	*Average values in precordial lead*				
	V	V	V	V	V
			Full term infant		
0 4 hr	27 0	44 4	42 0	9 0	—
1 day-1 wk	28 0	43 0	35 0	10 0	—
1 wk. 1 mo	21 0	37 7	29 8	11 8	—
1 3 mo	20 0	32 8	34 4	13 7	—
			Premature infant		
0-48 hr	7 39	17 17	14 94	9 00	4 78
48-96 hr	5 57	15 39	19 25	12 78	5 25
day 4 7	6 45	17 48	19 00	12 60	5 31
wk. 2	7 52	21 30	21 98	13 16	6 98
wk. 3	9 37	22 07	23 93	14 20	6 73
wk. 4 6	7 50	20 61	20 43	15 54	5 46
wk 6-9	9 47	20 07	21 03	17 20	7 10

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Table VI. Incidence of RST segment deviation in extremity leads

Age	Incidence in extremity leads					
	I	II	III	aVR	aVL	aVF
			Full term infant			
0-24 hr	3.13	15.6	25.0	9.4	0	9.4
1 day-1 wk	14.3	42.8	53.6	25.0	10.7	32.1
1 wk.-1 mo.	20.0	17.5	15.0	0.5	0.25	10.0
1-3 mo.	5.27	5.27	13.2	0	2.61	7.9
			Premature infant			
0-48 hr	33.3	33.3	88.9	22.0	33.3	66.7
48-96 hr	50.0	50.0	64.3	50.0	4.9	57.1
day 4-7	42.9	47.6	61.9	71.4	47.6	57.3
wk. 2	84.0	72.0	68.0	52.0	48.0	72.0
wk. 3	66.6	93.3	73.3	60.0	53.3	80.0
wk. 4-6	50.0	78.6	78.6	35.7	42.9	64.3
wk. 6-9	66.6	100.0	53.3	40.0	53.3	60.0

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Table VII. Incidence of RST segment deviation in precordial leads

Age	Incidence in precordial leads				
	V	V	V	V	V[illegible]
		Full term infant			
0-24 hr	25.9	51.9	80.0	7.4	—
1 day-1 wk.	50.0	37.5	91.0	12.5	—
1 wk.-1 mo.	41.7	25.0	75.0	8.35	—
1-3 mo.	23.1	3.85	75.0	11.55	—
		Premature infant			
0-48 hr	77.8	88.9	66.7	66.7	55.6
48-96 hr	78.6	64.3	78.6	71.4	42.9
day 4-7	66.7	66.7	80.9	71.4	71.4
wk. 2	88.0	56.0	84.0	60.0	96.0
wk. 3	86.7	46.7	60.0	86.7	93.3
wk. 4-6	64.3	57.1	78.6	42.9	71.4
wk. 6-9	93.3	33.3	26.7	66.6	86.7

From R. F. Ziegler: Electrocardiographic Studies in Normal Infants and Children, 1951. Courtesy of Charles C Thomas, Publisher, Springfield, Ill.

Wide variation in the electrical axis of the QRS complex and disturbances in impulse mechanism and in conduction were attributed to cardiovascular immaturity since they were seen without associated clinical heart disease.[1, 11] An increased

incidence of electrocardiographic abnormalities was reported in the younger premature infants in the first days of life

Regular sinus rhythm was usually present in the premature infant with a considerably lesser incidence of arrhythmias reported than in the full term baby Angeli on the other hand reported sinus arrhythmia to be characteristic and Nadrai noted frequent extrasystoles The electrocardiogram of the premature infant was usually described as having lower voltage than that of the full term infant this being most prominently seen in the QRS complex Engel's work did not confirm this Sebum reported the voltage of the electrocardiogram of the premature infant to be too low to obtain satisfactory records for analysis A decrease in the duration of all electrocardiographic deflections in the record of the premature infant was reported by Angeli Stoermer Thaon and Nadrai this was variously attributed to increased heart rate smaller cardiac muscle mass and cardiovascular immaturity

Gomirato Sandrucci and Crosato[4] observed no difference between the P wave of the premature infants and that of the full term infants whereas most other observers emphasized the prominent P waves (usually described as P pulmonale) in the records of premature infants Mader and Lanza and Stoermer's measurements of the Q T interval of the premature infant were within normal limits a prolonged Q T interval was more frequently commented upon Deviation of the S T segment from the isoelectric line associated with low voltage or abnormally directed T waves was commonly described

Much of the disparity noted above may be accounted for by the lack of uniformity in the electrocardiographic equipment used the small numbers of cases in most series the differences in the criteria for prematurity and the variations in the age of the premature infant at the time of the electrocardiographic recording

Discussion

We have without particular difficulty obtained satisfactory serial electrocardiographic records on 7 premature infants Analysis of these tracings shows some similarity to the characteristic electrocardiographic features in the records of full term infants right axis deviation of the QRS and frequent T wave inversion in the right and mid precordial leads However distinct differences are equally apparent

Although we are unable to offer logical and satisfactory explanations for these differences it seems of value to state a few possibilities which come to mind The P wave of the electrocardiogram of the premature infant was noted to be of significantly greater amplitude than that of the full term infant the greater pulmonary arterial pressure from the immature pulmonary vascular bed and the increased mechanical resistance due to incomplete expansion of the lungs may well be the responsible factors

The generally smaller QRS deflection seen in all electrocardiographic leads in the premature infant may be explained by the relatively smaller cardiac mass available to generate electrical activity

Quite obviously any change in cardiac configuration can influence the spatial vector pattern reflected in the electrocardiogram The wider range of values for the electrical axis of the QRS complex and the fewer and smaller Q waves observed in the premature infant may in some way be related to the globular cardiac configuration so often seen in the premature baby

RST segment deviation from the isoelectric line is much more pronounced in the premature infant The question is raised whether this repolarization abnormality is due to the somewhat more rapid heart rate of the premature infant or to actual myocardial anoxia resulting from an immature respiratory system

The T waves of the premature infant particularly in Leads I aVL and V were opposite in direction to those observed in the full term infant This again is explicable either as a secondary T wave change (the QRS differing in the premature and the full term infants) or as a primary repolarization abnormality related to pulmonary vascular immaturity and hypoxia An alternate or additional factor both in the RST segment and T wave changes is the somewhat abnormal electrolyte pattern

of the premature infant probably secondary to the immaturity of renal function

Conclusion

In a preliminary study of the characteristics of the electrocardiogram of the normal premature infant several differences from the electrocardiogram of the full term infant are apparent. The electrocardiogram of the normal premature infant is seen to have (1) greater P wave amplitude (2) wider range of the QRS electrical axis (3) smaller QRS amplitude (4) fewer and smaller Q waves and (5) greater S T—segment deviation

Complete statistical analysis of our data has not been permitted because the number of individual studied was relatively small and these data would therefore have limited significance. However the authors have more detailed numerical values for the several components of the electrocardiogram of the premature infant

Our appreciation is due to Mrs Rose Ann Mangum and Mrs Mildred S Barber Cardiology Technicians for their technical assistance

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The loud musical diastolic murmur of an abnormal rheumatic chorda

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McKusick in his excellent monograph on cardiovascular sound has defined musical murmurs as murmurs presenting a quality best defined by the proved ability to represent the murmur by conventional musical notation In the spectrogram musical features are characterized by the presence of harmonics—the most objective definition of musicality and in the conventional phonocardiogram musical murmurs are often recognized by their rapid high frequency vibrations

Musical murmurs usually occur in systole and originate from the aortic valve the mitral valve or extracardiac sources Musical diastolic murmurs on the other hand seldom occur except in valvular deformities The mitral valve has very rarely been implicated McKusick described one patient cured of subacute bacterial endocarditis who had an unusual systolic and diastolic apical murmur and another who had a musical presystolic murmur Calo[1] reported a musical apical presystolic murmur in a patient who had syphilitic aortitis with aortic incompetence

In this report we describe a patient who had a striking musical diastolic and presystolic murmur superimposed on the conventional murmurs of mitral stenosis The murmur sounded like the vibration of a musical string instrument It was unaffected by mitral valvular operation and was attributed to an abnormal thickened rheumatic chorda tendinea strung across the orifice of the mitral valve

Case history

V L a 28 year-old Coloured male was first seen in February 1957 complaining of progressive effort dyspnea which had been present for 1 year He had been compelled by his symptoms to change his occupation from bricklayer to petrol attendant but was not sufficiently disabled to warrant an operation

On examination there was no evidence of heart failure the jugular venous pressure was normal the pulse felt small and the blood pressure was 130/80 mm Hg The apex was normal in situation and quality There was a long diastolic rumble with presystolic accentuation and a Grade 2/6 long mitral systolic murmur The opening snap was barely audible and the first sound was not accentuated suggesting calcification of the mitral valve This latter condition was confirmed on screening An ejection sound was present at the base and fourth left intercostal space with a high pitched cooing down short early diastolic murmur of no apparent hemodynamic significance The electrocardiogram showed marked left atrial hypertrophy and on x-ray examination the left atrium and pulmonary arteries were observed to be moderately enlarged and the left ventricle full sized Operation was postponed

Within 7 months his condition had deteriorated considerably cough hemoptysis and orthopnea developed and required digitalization From then

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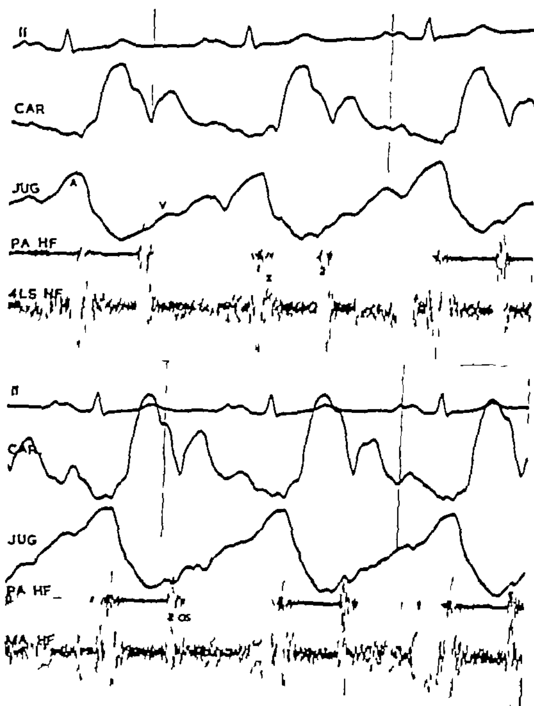


Fig. 1. High frequency phonocardiograms taken at the pulmonary area (*PA*), fourth left intercostal space (*4LS*) and mitral area (*MA*) with synchronous carotid artery (*CAR*) and jugular venous tracings (*JUG*). At the mitral area the high pitched musical murmur is well shown. The vibrations are very rapid but evenly spaced and although they vary in intensity from cycle to cycle presystolic accentuation is always present. The murmur radiates to the fourth left intercostal space and pulmonary areas where it has been recorded. The presystolic murmur ceases before the slightly delayed first heart sound and the P-R interval is full. *Mid diastolic vibrations are also present. A pansystolic murmur and opening snap are also shown. The high fre*quency musical murmur is superimposed on the usual low frequency diastolic murmur of mitral stenosis. At the fourth left intercostal space in addition to the musical murmur an early diastolic murmur of aortic incompetence has been recorded. A pulmonary ejection click (*X*) and pansystolic murmur are also present. At the pulmonary area the sound and murmurs have been attenuated. Splitting of the second sound is present as well as an opening snap. The pulmonary ejection click and musical diastolic murmur are also recorded.







Fig 2 Appearance of the mitral valves left atrium and left ventricle at necropsy A Viewed from the left atrial cavity The stenosed incompetent mitral valves are well shown with fusion of the commissures and calcification of the cusps The abnormal thickened chorda is stretched across the orifice of the valve *B* Viewed from the left ventricular cavity The probe ([illegible]) has been passed through the orifice of the mitral valve into the left ventricle The hypertrophied and dilated left ventricle shows with an abnormal papillary muscle from which the thickened abnormal chorda runs to the mitral valve leaflet The diseased mitral and aortic valves are also visible C This typical chorda has been put on the stretch by slightly displacing the papillary muscle with a pin The abnormal position of this thickened chorda results in it being in the direct line of the flow of blood from left atrium to left ventricle The normally situated chordae and papillary muscles show the typical rheumatic thickening shortening and cross-fusion The thickening and slight fusion of the aortic valve cusps is also shown

on until he underwent operation 3 months later the auscultatory findings were confusing and difficult to interpret. The common dov murmur altered in timing and quality varying considerably in intensity from cycle to cycle (Fig. 1) and also in position in diastole. To the ear there were three distinct diastolic murmurs (not readily differentiated on the phonocardiogram)—an early diastolic murmur of aortic incompetence, a mid-diastolic murmur of mitral stenosis and a high frequency violin string twang superimposed on the latter but varying in intensity and situation. It was always loudest in presystole (Fig. 1) stopping before the first sound but was also superimposed on the mitral mid-diastolic murmur. In addition systolic murmurs were present at the mitral and tricuspid areas suggesting mitral and tricuspid incompetence.

Operation was advised in view of the progressive nature of the symptoms and the signs which suggested dominant stenosis although some degree of incompetence was anticipated. At operation the valve was slit like, measured 1.3 square centimeters and was encrusted with calcium particularly toward the posteromedial commissure. A distinct *regurgitant jet was present but there was no gross* reflux and the valves were regarded as being moderately fibrosed. The anteromedial cusp ballooned out well and digital splitting was achieved by the padded finger; a valve orifice of over 5 square centimeters was obtained associated with only slight increase in the regurgitant jet. Left atrial pressure fell from 25/18 to 18/11 mm. Hg with little change in pulse form. Histologic examination of the left atrial biopsy specimen showed a number of active Aschoff nodes suggesting recent inflammation. In the *lung biopsy specimen the pulmonary* arteries were thick walled and a vessel partially occluded by organized thrombus was found.

The immediate response to the operation was satisfactory. Three months later he had improved considerably despite the persistence of postoperative atrial fibrillation. On auscultation the variable high pitched twanging diastolic murmur was superimposed on the aortic and mitral diastolic murmurs but the presystolic murmur had disappeared. The mitral systolic murmur had increased in intensity.

The unusual auscultatory findings were attributed to an atypical thickened chorda which straddled the orifice of the mitral valve and which vibrated during the flow of blood from the left atrium to the left ventricle.

Digitalization was followed by several attempts at correction of the arrhythmia with quinidine without success. The drug was abandoned after the development of a rapid regular tachycardia due to 1:1 rhythm with aberration.

Thereafter the condition of the patient deteriorated rapidly *and within a month he was readmitted* for control of severe congestive cardiac failure with a jugular venous pressure of over 25 cm., a four finger tender pulsating hepatomegaly, ascites, and signs of mitral stenosis, aortic incompetence and mitral and tricuspid incompetence. After initial response to treatment he became refractory to diuretics, developed gross intractable heart failure and died 17 months after operation.

Necropsy revealed gross congestion of all organs with subcutaneous edema, ascites, pleural effusion, pulmonary edema, and cardiac cirrhosis. The heart weighed 705 grams; both atria were hypertrophied and dilated. The left ventricle was dilated and probably hypertrophied and the right ventricle was markedly hypertrophied and dilated with severe atheroma of the pulmonary tree.

The mitral orifice was an oval narrow stenosed cleft which admitted the tip of one finger and had rigid calcified cusps. The site of the previous operative splitting could not be determined. From the atrial aspect (Fig. 2A) a thickened abnormal chorda tendinea could be seen stretched across the mitral orifice. From the ventricular aspect the chordae were considerably thickened and shortened and the abnormal chorda (Fig. 2B) could be seen stretched across the inflow tract of the dilated left ventricle. The aortic cusps (Fig. 2C) were slightly thickened and there was fusion of the commissures between two of the cusps without significant stenosis or incompetence, however.

Discussion

We have reported on a patient in whom musical mid-diastolic and presystolic murmurs were heard and recorded phonocardiographically during life; the murmurs were associated with an unusual malformation of a chorda tendinea found at necropsy. The patient developed all the signs and symptoms of severe obstructive mitral valvular disease with trivial incompetence. On the first examination the musical murmur was mistaken for a "cooing dove" murmur of aortic incompetence. Re-examination, however, revealed a distinctive murmur occurring in mid-diastole and presystole. The cadence was that of a plucked string of a musical instrument varying from cycle to cycle both in position and intensity but always diastolic. Although presystolic accentuation was present, the sound was clearly separated from the first heart sound. At mitral valvotomy no pericardial disease was detected and no extracardiac cause for the unusual observations could be found. Severe rheumatic mitral valvular stenosis with slight incompetence was recognized and commissurotomy was performed. After the operation there was no alteration in the character of the musical murmur except for the disappearance of the presystolic accentuation with the development of atrial fibrillation. The improvement after operation was short lived and necropsy 17 months later revealed severe chronic congestive cardiac failure with unrelieved mitral stenosis, some mitral incompetence and slight involvement of the aortic valve.

The murmurs were attributed in life to an abnormal attachment of a chorda tendinea which straddled the orifice of the mitral valve and this was confirmed at necropsy

Huchard[4] in 1893 was the first to describe a musical murmur due to aberrant tendons crossing the stream of blood flow Because these murmurs appeared only later in life it was postulated that the aberrant tendons had first to be tautened by ventricular dilatation before being able to cause murmurs Murmurs produced in this fashion have been likened to the sound produced by the aeolian harp[1] Huchard's murmur however was systolic in time Continuous musical murmurs have been attributed to tensing of an abnormally developed Chiari network [7] Diastolic murmurs of mitral origin are even rarer most diastolic murmurs are either aortic or extracardiac in origin

In our case it is postulated that a congenitally abnormal chorda was thickened shortened and tautened by the rheumatic process This resulted in a shortened chorda strung across the abnormal stenosed orifice of the mitral valve During the flow of blood from the left atrium to the left ventricle the chorda tautened by the dilating ventricle was thrown into vibration and produced a sound like the plucking of a harp string An increased flow of blood during contraction of the hypertrophied left atrium produced accentuation of the murmur The variability of the murmur is presumably attributable to change in position of the chorda from cycle to cycle and possibly also to the change in the degree of its tautening by the dilating ventricle during diastole The absence of a murmur during systole can be explained by the postulate that the regurgitant stream of blood from the left ventricle was directed away from the chorda Straddling the mitral orifice as it did the chorda could hardly fail to be involved during forward flow from left atrium to left ventricle

Summary

A case of rheumatic heart disease with dominant mitral stenosis is presented in which a peculiar musical mid diastolic and presystolic murmur was heard and recorded phonocardiographically

The murmur was characterized by the peculiar tonal qualities simulating the vibrations produced by a stringed instrument such as a harp The murmur varied in intensity from cycle to cycle and also in position and was maximal in presystole At necropsy an abnormal anatomic chorda tendinea pathologically thickened by rheumatism was found to be strung across the mitral orifice

The musical sounds in diastole were attributed to vibration of the abnormal chorda during the flow of blood from the left atrium to the left ventricle

We wish to thank Dr P Camerley for his surgical findings Dr M Sacks for the pathologic examination and the Superintendent Dr J Burger for his permission to publish this report

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Parasystole with a rapid ventricular center

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Parasystole is of special interest among the disturbances of ectopic impulse formation. First, a parasystolic arrhythmia is of clinical importance because the ventricular form usually indicates the presence of organic heart disease. Second, parasystole, although not rare, is frequently overlooked because it is not differentiated from extrasystole. Third, the mechanism of parasystole needs to be explained more satisfactorily. In this paper we have collected examples of parasystole from 8 patients which contribute to the better understanding of its mechanism.

An important feature of parasystole is the phenomenon that the parasystolic center from which ectopic impulses arise is not influenced by the spread of normal impulses over the heart. This requires an explanation since according to a principle of cardiac physiology all fibers of the heart are depolarized by the spread of an excitation. It has been assumed that the center is protected by a "block zone." The block prevents an outside stimulus from disturbing the parasystolic center. This hypothesis was accepted only after certain experimental studies established two facts. One, parasystole could be induced in the dog heart and the parasystolic center was not disturbed by the basic rhythm. Two, the production of a unidirectional block which permitted impulses to be transmitted in a strip of muscle in only one direction demonstrated that impulses formed in a center may activate the heart while the center remains unaffected by the normal rhythm. Unidirectional block, however, which is seen only under very special conditions, would be difficult to postulate during the prolonged periods over which parasystole has been observed in some patients.

Although the concept of a protected ectopic parasystolic center is fundamental to explain parasystole, the term "block" was said to be inappropriate because there is no evidence of a disturbance in conduction usually implied by this word. Instead, the term "protection" of the parasystolic center has been proposed. This protection was ascribed to the high rate of formation of impulses in the center. Experiments on the dog heart made hypodynamic by quinine have shown rates of impulse formation up to 300 per minute in a center induced by mechanical or electrical stimulation with only every second impulse propagated. In these experiments a 2:1 exit block usually existed. Because of the rapid formation of stimuli, the center was refractory to outside impulses.

Later studies sought to explain protection by a decreased excitability of the center or by infra-threshold impulses. According to this view, a parasystolic arrhythmia would depend only on the relation between the strength of the impulse and the excitability of the center. This explanation is not entirely satisfactory because it fails to

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Fig. 1 Observ tion 1 The tracings were taken in Lead II They how a entricular tachycardia hich interrupted in A by mus beats measurements how that these mus beats do not disturb the activity of the ectopic center I C and D the inus rhythm sometimes overtakes the tachy cardia after the manner of di sociation with interference.

indicate why a conducted impulse would not completely depolarize a parasystolic center especially one in which slow dias tolic depolarization s characteristic feature of impulse formation had already begun to depolarize the cell membrane On the basis of our present knowledge supported by the present study we believe that the most logical explanation for protection remains our original one viz rapid forma tion of impulses in the parasystolic center

Observations

Observation 1 This 50 year old man with diabetes coronary sclerosis and congestive heart failure while on a maintenance dose of 0 1 Gm of digitalis daily developed a rapid parasystolic center protected from the sinus beats Fig 1,A (Lead II) shows a ventricular tachycardia with a rate of 110 beats per minute The individual ectopic beats are not conducted in reverse manner back to the atria Successive ectopic periods measure 52 56 55 56 56 54 54 56 54 Sinus rhythm soon overtakes the ectopic rhythm with two sinus beats which are followed by a combination beat and the reappearance of ectopic beats The interval between the two ectopic beats separated by the sinus beats measures 222 or exactly four ectopic periods of 55 5 each

The same pattern reappears in B C and D of Fig 1 taken several days later In both C and D a sinus beat activates at least a portion of the ventricles In both instances the interval between the two ectopic beats next to the summation beat equals two ectopic periods

Observation 2 This 67 year old man who had an inferior wall infarction as indicated in the standard leads in Fig 2,A developed a rapid ventricular center protected from the sinus rhythm as in parasystole This ventricular tachycardia with a rate of 115 per minute was registered in Leads II and III (B and C of Fig 2) 6 days after the infarction As in the first observation the ventricular ectopic beats were not con ducted back to the atria and sinus beats occasionally reached the ventricles (Fig 2 D and E) Successive ectopic intervals measure between 52 and 55 When sepa rated by sinus or combination beats the interval doubles becoming 104 107 105 108 104 and 106 that is two ectopic intervals It is obvious therefore that the ectopic center is protected from the sinus beats and that we are dealing with a parasystole with a rapid center

Observation 3 This 88 year-old man with coronary sclerosis and atrial fibrillation controlled by 0 2 Gm of digitalis daily demonstrated both a ventricular parasys tole and exit block All tracings w

*These figures about hundredths f second



Fig. 2. Observation 2. *A* shows evidence of an inferior wall infarction in the three standard leads. A ventricular tachycardia appeared (*B*) with a rate of 115. Here again, as in Observation 1, sinus beats occasionally succeed in reaching the ventricles (*C* and *D*); they do not disturb the activity of the ectopic center.

registered in Lead II. In Fig. 3,*A* a ventricular tachycardia follows two beats conducted from the atria. The interectopic periods of the tachycardia which vary between 62 and 73 signify rates between 96 and 82 beats per minute. The successive ectopic periods measure 73, 69, 67, 65, 64, 63, 62, 62, and 62. The rate of the ectopic center during the uninterrupted ectopic rhythm gradually increases. This phenomenon is not a rare observation in parasystole and has been described repeatedly. In Fig. 3,*B* the tachycardia ends and groups of bigeminy without fixed coupling appear. Ectopic intervals measure 60, 61, 62, and 60. After the tachycardia the ectopic distances measure 187, 182, and 187 (3 × 62 or 60.5). The last ectopic beat is not shown.

In Fig. 3,*C* a long pause occurs measuring 263 (or 4 × 66) which contains an extrasystole and a conducted beat. Interectopic periods between 64 and 68 then follow.

In the subsequent tracings of Fig. 3 (*D* to *G*) the pauses which contain conducted beats are always a multiple of the basic ectopic interval. During these pauses an exit block must exist since ectopic impulses fail to activate the ventricles even if such impulses appear outside of the refractory phase.

The tracings in Fig. 4 were obtained from this patient on the same day. In *A*, taken in Lead I, the first impulses after a long interval without ectopic beats appear at a slow rate with periods of 72, 70. The rate rapidly increases with successive periods shortening to 68, 66, and 64. Tracings *B* through *E* demonstrate an exit block. In *E* a beat representing the summation of an ectopic beat and a conducted beat is followed by ectopic intervals of 66, 62, 62, 6?, and 38. The sudden halving of the interval suggests that the ectopic center actually works at a rate of about 158 and that most of the ectopic intervals result from a 2:1 exit block.

Observation 4. The presence of exit block is also suggested in the tracings (Fig. 5) obtained from a 48 year old nondigitalized hypertensive man admitted with an acute hemiplegia. In addition to sinus rhythm extrasystoles and late ectopic beats the electrocardiogram sl ... rked intra ventricular block. In ... of ectopic intervals of

center working at a rate of 140 halved by a 2:1 exit block to 70. In the beginning of *D* recorded in Lead V three ectopic beats the last deformed by a summation with a sinus beat present a rate of 70 with interectopic intervals of 84. After two sinus beats—the first is slightly deformed by summation—two ectopic beats occur separated by an interval of 42 which represents a rate of 140. Likewise the interval of 215 (5 × 43) between the third beat in *D* and the next ectopic beat suggests an ectopic rate of about 140 partially suppressed by an exit block. Tracing *E* of Fig. 5 shows an



Fig. 3. Observation 3. All tracings were taken in Lead II. There is atrial fibrillation (A) and the patient was under digitalis therapy. The tracings show a rapid ventricular ectopic rhythm and the intervals without ectopic beats are multiple of the ectopic interval. There is a 2:1 exit block in several tracings.

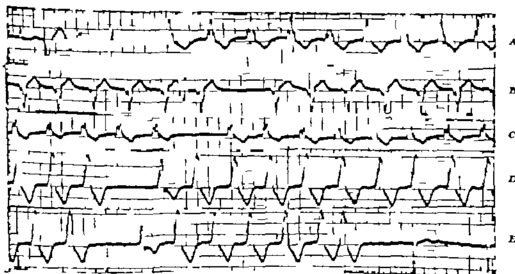


Fig. 4. Observation 3. The tracings were taken in Leads I, VL, and V; tracings *D* and *E* which are continuous were recorded in Lead V. The tracings show exit block with parasystole and sudden premature ectopic beat in *E*.

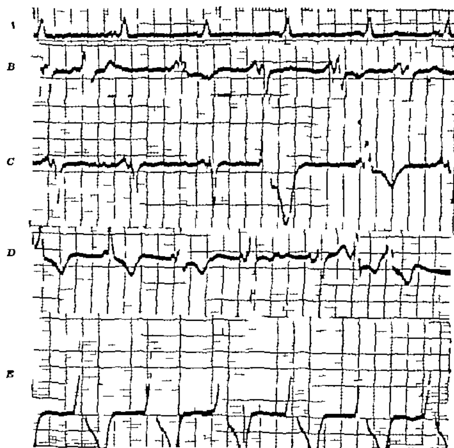


Fig 5 Observ tion 4 The standard leads show an intra entricular block and premature ectopic beat I D (Lead V_2) ectopic beats ppear The intervals between the first three are 86 and 84 the interval between the last two is 42 This suggests th t center is active with an ectopic interval of about 42 and that in the beginning of *D* and *E* (Lead V) 2 1 exit block prevails

ectopic rhythm with an interval of 84 corresponding to a rate of 70 which could easily represent a 2 1 block

Unfortunately no further tracings were obtained from this patient The arrhythmic pattern indicates a parasystolic center with a rapid rate of 140 subjected to an exit block which reduces the ectopic rate to 70

Observation 5 This 80 year old man with coronary sclerosis exhibited a parasystole with an ectopic rate of about 80 which on carotid pressure not only slowed but at times exhibited extrasystoles coupled to the automatic beats

In tracing *A* of Fig 6 combination and normal sinus beats are sandwiched between ectopic ventricular tachycardias Although the patient did not receive digitalis the P R is prolonged to 0 24 The ectopic intervals of 78 74 and 73 represent a heart rate between 77 and 82 The interval between the fourth and tenth complexes measures 456 or 6 × 76 In tracing *B* in which only a single sinus beat is seen

Table I

73—219	(3 × 73)
72—218	(3 × 72 5)
72—218	(3 × 72 5)
73—520	(5 × 74 5)
74—448	(6 × 74)
77—314	(4 × 78)
74—298	(4 × 74)
79—382	(5 × 77)
76—306	(4 × 76)
77—308	(4 × 77)
6—304	(4 × 76)
76—306	(4 × 76)
6—304	(4 × 76)

Th first fig re presents th ectopic interv l which we directly mea ured in Observation 5 d th h duration of lo terval is d by time be

the interval between the ectopic beats adjacent to the sinus beat is 117 or 2 × 73

In long tracings taken from this patient ectopic intervals varied between 72 and 79 on different days Often several sinus beats replaced the ectopic beats, causing long intervals free of ectopic beats All of them are seen in Table I which gives

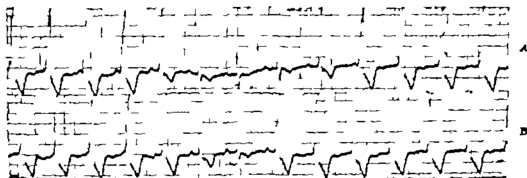


Fig 6 Observation 5 Both tracings show an ectopic rapid rhythm interrupted by sinus beats The long interval without ectopic beats which is created by the sinus beat measures a simple multiple of an ectopic period

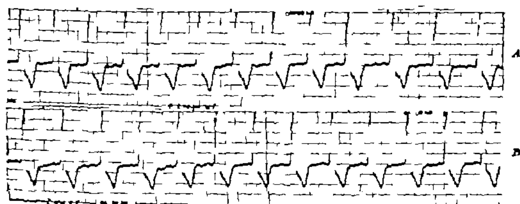


Fig 7 Observation 5 The tracings are continuous Pressure on the carotid sinus as indicated by the horizontal black line at the bottom of the tracing slows the ectopic ventricular rhythm

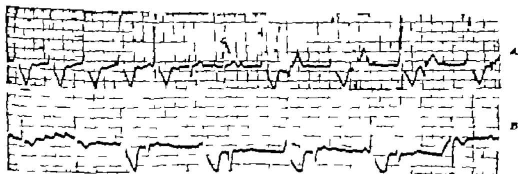


Fig 8 Observation 5 Carotid pressure during sinus rhythm causes the appearance of a slow ectopic rhythm with extrasystoles which appeared bound only to the ectopic beats and never to sinus beats

first the ectopic interval is measured just before and after the sinus beats and then the duration of the pause between two ectopic beats filled by sinus beats.

Figs. 7 and 8 show the effect of carotid sinus pressure. Slowing is demonstrated in *A* and *B* of Fig. 7 in which the interectopic interval increases from 72 to 85 during right carotid pressure (*black line*) and returns to 72 upon the release of pressure. (*A* and *B* of Fig. 7 are continuous.)

The other effect of carotid pressure, the appearance of extrasystoles with fixed coupling to the ectopic beats, is seen in Fig. 8. In *A* of Fig. 8, after an ectopic tachycardia with an interval of 71, carotid pressure elicits ventricular extrasystoles. The ectopic interval measures 132, whereas the interval between the extrasystole and the following ectopic beat is 82 to 84. On the next day carotid pressure during sinus rhythm (tracing *B*) again evoked an ectopic rhythm with extrasystoles bound only to the ectopic beats. The interval between ectopic beats is 161 to 168; the postextrasystolic interval is 113. Similar extrasystoles bound only to the ectopic beats appeared on two subsequent occasions during carotid sinus pressure.

Observation 6. Another example of parasystole was noted in a 22-year-old woman with a pulmonary stenosis and effort angina. When the patient received no medication the electrocardiograms usually showed ectopic ventricular beats interrupted by sinus beats. The ectopic interval of 68 (Fig. 9) represents a rate of 86, whereas the rate of the sinus beats, which reflect a marked right ventricular hypertrophy, is 92 per minute. *Both rhythms dominated the ventricles* for a few beats simultaneously with the frequent appearance of combination beats. Intervals between ectopic beats separated by sinus beats were always a multiple of the interval between two successive ectopic beats.

In Fig. 10, taken after the patient had been without medication for 10 days, the ectopic intervals continue to be a multiple of the shortest interectopic distances. In this tracing, the ectopic intervals vary between 84 and 88. The sinus rate is 75 with a P-R interval of 80. In Lead I (Fig. 10) the ectopic intervals measure 170, 176, 88, and 164, and in Lead II they measure 80, 160, 254, 160, and 164—all multiples of the shortest ectopic interval.

On occasion the parasystole would disappear without the patient having received medication and extrasystoles would appear with fixed coupling. In these instances the first interectopic interval was always shorter than the succeeding ones. Quinidine and digitalis abolished the parasystole and led to a bigeminal rhythm with fixed coupling.

Observation 7. Fig. 11, registered in Lead III, was obtained from a 93-year-old woman with coronary sclerosis. In addition to an atrioventricular block, the tracing shows ectopic beats with intervals measuring successively 164, 52, 156, and 156 (3 × 52). This measurement suggests an ectopic rate of 115 per minute, corresponding to the shortest interectopic intervals of 52. The longer intervals, which are multiples of this distance, could easily be attributed to an exit block.

Observation 8. This 89-year-old man complained of exertional dyspnea, anorexia, meteorism, and an irregular pulse. Mildly diabetic (on 18 units of NPH insulin daily), he had sustained an anterior lateral wall myocardial infarction 6 years previously, at which time ventricular beats with varying coupling were noted. Prior to the registration of the electrocardiograms discussed below (Figs. 12 and 13) his physician had administered 0.1 Gm. of digitalis daily, hydrochlorothiazide, and ammonium chloride.

Fig. 12 shows numerous ectopic beats interrupting the sinus beats. The latter exhibit a P-R interval of 0.25 second and the pattern of left ventricular hypertrophy. The intervals between the ectopic beats in tracing *A* (Lead I) are 154, 102, 167, 85, 162, 90, and 180; in *B* (Lead II) they are 126, 42, 83, 250, and 254; in *C* (Lead aVF) they are 39, 74, 127, 46, 78, and 216; in *D* (Lead V_4) they are 40, 86, 126, 58, 69, 214, and 254; and in *E* (Lead II) they are 268, 221, 47, 230, 41, and 127. These intervals suggest that a center which forms impulses at a rate of 150 per minute (as indicated by the interectopic interval of 40) functions with a 2:1, 3:1, and 4:1 exit block to explain the long intervals. Another feature of parasystole, the combination beat, is seen in the fourth ventricular complex of tracing *B*.

Occasionally impulses formed in the ectopic center are conducted with a delay to the ventricle so that the interectopic interval is slightly prolonged. The following interval becomes proportionately shorter. Thus in *C* and *D* of Fig. 12 the sum of a short interval and the succeeding consecutive long ectopic interval equals the sum of the longer preceding or following intervals. The sum of these intervals in Fig.

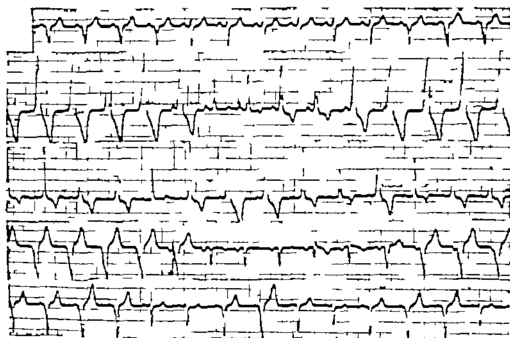


Fig. 9. Observation 6. Simple parasystole with rapid ectopic center. The sinus beat shows evidence of right ventricular hypertrophy. The tracings were taken in the three standard leads followed by Lead V and V.

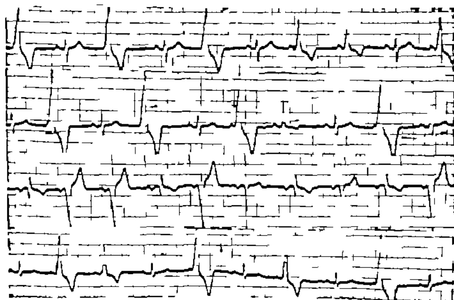


Fig. 10. Observation 6. The tracings were taken in Leads I, II, V and V. There is simple parasystole with combination beat.

Table II. Summary of data obtained in the 8 instances of parasystole with a rapid rate of the ectopic center

Observation	Age (yr.)	Diagnosis	Rate	Salient features
1	50	Coronary sclerosis	109	Rapid ectopic center protected from sinus beats
2	67	Inferior wall infarction	109–115	Rapid ventricular center protected from sinus rhythm
3	88	Coronary sclerosis, atrial fibrillation	96–8 94–81 158	Exit block
4	48	Hypertension, hemiplegia	142	Exit block 2:1
5	80	Coronary sclerosis	76–82	Carotid sinus pressure slowed ectopic rate 83-71 and produced extrasystoles bound to automatic beats
6	22	Pulmonary stenosis, effort angina	86	Parasystole
7	93	Coronary sclerosis	115	
8	89	Coronary sclerosis	150	Exit block

12 *C* totals 123, 127, 124, and 246 (2 × 123). These and similar calculations observed in many of the long tracings recorded in this patient demonstrate that the formation of ectopic impulses takes place in a rapidly acting parasystolic center.

Of great interest and importance in this patient is the inhibition of the sinus beats and the consequent emergence of the full ectopic rhythm by carotid sinus pressure. Two observations with carotid pressure taken 10 days apart are reproduced in the pairs of continuous tracings of Fig. 13 *A* and *B* and *C* and *D*. Although the duration of carotid pressure is roughly indicated by the horizontal black line, pressure was actually applied 3 seconds before the black line registered. Seven additional applications of carotid pressure produced the same effect, viz., inhibition of sinus beats save for occasional P waves and the development of an ectopic rhythm free from any disturbance. Here again, as in Fig. 12, short and long interectopic intervals occur. The successive interectopic intervals in *A* and *B* of Fig. 13 measure 261, 44, 84, 129, 79, 41, 127, 126, 126, 126, 127, 51, 73, 124, and 248. In *C* and *D* of Fig. 13 these intervals measure 41, 83, 128, 56, 65, 122, 58, 60, 123, 43, 80, 123, 129, 124, 40, 78, 124, 41, 80, and 246. If, as in Fig. 12, we add the short and the following ectopic intervals, we obtain the following successive intervals: 261 (2 × 130.5), 128, 129, 125, 127, 125, 126, 126, 127, 124, 124, 248 (2 × 124). In Fig. 13 the intervals obtained in the same manner are 124, 128, 121, 122, 128, 123, 123, 123, 129, 124, 128, 124, 121, and 246 (2 × 123).

This study illustrates both the occurrence of a rapid ectopic parasystolic center exhibiting a 2:1 and 3:1 exit block and the emergence of a full ectopic rhythm during carotid sinus pressure. The conduction of some of the ectopic impulses is delayed in the ventricle so that beats which appear late are followed by a correspondingly shortened interval.

Discussion

These 8 observations summarized in Table II present examples of parasystole with rapid rates of formation of impulses in the ectopic center. In some instances, as in Observations 3, 4, 7, and 8, a 2:1 and 3:1 exit block is evident. Ectopic formation of impulses in the ventricles, even with a slow sinus rate, leads to a ventricular paroxysmal tachycardia if the ventricular impulses are conducted in reverse manner to the atria or if the rate is rapid. Simple parasystole may develop in the absence of reversed conduction, provided that the ectopic rate is rapid and exit block exists.

That parasystolic centers with a rapid rate occur is borne out not only by these observations but by a review of reports in the literature. Rapid rates were noted in one of the original papers on parasystole,[9] although the interpretation of these cases has been questioned. In 1932 Fulltschek

and Scherf[4] reviewing 11 cases of parasystole found that in 2 instances the rate was over 80 per minute and in the other cases between 34 and 61 per minute. Vedoya[14] observed a patient with a parasystolic rate between 133 and 138 during sinus rates of 109 to 133. Katz and Pick described a patient with a sinus rate of 75 to 95 whose ectopic rate was 88 (see their Fig. 196). Gaspary[8] recorded a parasystolic rate of 120. In another observation[8] the rate of an ectopic atrioventricular nodal parasystolic center increased from 83 to 166 proving the presence of a 2:1 exit block.

The inference that a 2:1 or 3:1 exit block obtains in most cases of parasystole

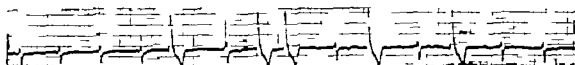


Fig. *11.* Observation 7. Ectopic beats in Lead III with ectopic intervals of 164, 52, 156, 156, and 156. This suggests that the longer intervals are the expression of 3:1 exit block.

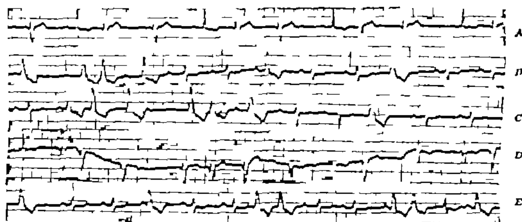


Fig. *12.* Observation 8. Tracings *A* through *E* represent Lead I, II, V_F, V, and II. The tracings show parasystole with exit block. Details are discussed in the text.

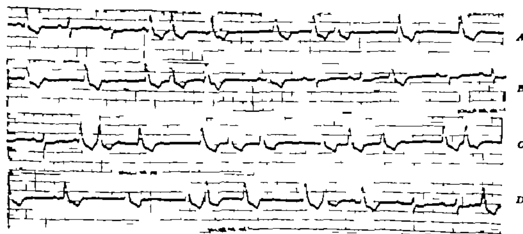


Fig. *13.* Observation 8. All tracings were recorded in Lead II. *A* and *B* as well as *C* and *D* are continuous. Carotid sinus pressure in both pairs of tracings suppresses the sinus rhythm and permits the undisturbed appearance of the parasystolic rhythm. Details are discussed in the text.

obviates the necessity of postulating the presence of a protection block. A sudden doubling of the ectopic rate, even if only for one beat, as in Observations 3, 4, and 7, and the rates noted in animal experiments quoted above suggest that at least in some instances of parasystole the actual rate of formation of impulses is rapid. Exit block merely makes it appear that the automatic rhythm is slow. If a center fires off impulses rapidly, it will be refractory to other impulses. We have no way of knowing whether all ectopic intervals measured directly in these tracings are not the expression of a 2:1 block. It is also possible that the ectopic center develops oscillatory potentials with a rate of about 300 and that only every second one reaches threshold values. Thus in explaining parasystole recourse need not be taken to theories which contradict known physiologic laws.

In experiments on dogs parasystole can be provoked by focal application of veratrine on the ventricles of the exposed heart[8] and by short mechanical or electrical stimulation of the ventricles after previous intravenous administration of quinine and atropine. In all these instances the rate of the ventricular parasystolic center is rapid.

Several observations indicate that the parasystolic center differs from the physiologic deeper ventricular centers. The latter function with a slow rate of automatism, as demonstrated by escaped beats and idioventricular rhythms. The rate in the observations described in the present paper is too rapid to be considered as the expression of a physiologic but protected automaticity. Conversely, in atrioventricular or nodal parasystole the rate may be far slower than the anticipated rate of formation of impulses at these centers. Consequently, these forms of parasystole must also be assumed to be caused by an abnormal kind of impulse formation.[3]

Another observation which sets the parasystolic center apart from the physiologic activity of deeper centers is the slowing of the ectopic rhythm in parasystole by carotid sinus pressure.[4] This slowing of parasystolic centers suggests that they are very sensitive to small amounts of acetylcholine. Normal ventricular centers rarely respond to the vagal effect of carotid pressure.[4]

The appearance of ventricular extrasystoles bound only to automatic ectopic beats and not to conducted beats, as in Observation 5 after carotid sinus pressure, has been described before[4] but remains unexplained.

All patients described in this presentation suffered from organic heart disease.

The presence of a center of rapid impulse formation in conjunction with a supernormal phase of excitability may lead to extrasystoles with constant or almost constant coupling.

Since this paper was submitted for publication, 3 more instances of parasystole with sudden temporary doubling of rate were observed.

Summary and conclusions

Parasystole was observed in 8 patients with the rate of the ectopic center varying between 96 and 150 beats per minute.

In 3 instances the rate of the ectopic center suddenly doubled for one beat, suggesting the presence of a 2:1 exit block in the other tracings. In one patient a 3:1 exit block existed.

The possibility is discussed that the ectopic rate in many clinical instances of parasystole actually is high and that a 2:1 or 3:1 exit block gives the impression of a slow ectopic center.

Assuming the presence of a rapid ectopic center, we need not consider the hypothetical action of a protection block.

One patient showed a clear exit block. Another patient revealed slowing of the automatic rate of the ectopic center by carotid sinus pressure and the repeated appearance of ventricular bigeminal rhythm during carotid pressure, with the extrasystoles bound only to the ectopic beats and not to sinus beats. In addition to 2:1 and 3:1 exit block, one patient showed a delay of the spread of the ectopic impulses from the center to the ventricles.

These observations make it improbable that the ectopic activity in parasystole represents simply the expression of the normal automaticity of a ventricular center. An abnormal rapid kind of impulse formation seems more probable. Therefore, the separation of parasystole from rapid ectopic tachycardias is less sharp; the presence or absence of an exit block makes the difference.

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The genesis of the normally split first heart sound

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In spite of the remarkable progress in phonocardiography—including intracardiac and extracardiac techniques—there is still some disagreement concerning the genesis of the two major components of the normally split first heart sound. This is emphasized in a recent paper by Luisada.[30]

Without regard to pathologic conditions (i.e., systolic clicks), two contradictory theories are under discussion to explain the normally split first heart sound. Although there is general agreement in the interpretation of the *first major component* of medium-high frequency vibrations, which is related by nearly all authors to closure of the left-sided atrioventricular valve (or to the normally simultaneous rapid rise in left ventricular pressure), some authors since Potain[39] (1866) explain the *second major component* as being due to closure of the tricuspid valve (Dock,[6] Wolferth and Margolies,[44] Leatham,[27] McKusick,[33,34] Reinhold and Rudhe,[41] Braunwald and Morrow[3]) in contrast to another group which believes it to be due to opening of the aortic valve or to left ventricular ejection (Orias and Braun Menendez,[37,38] Rappaport,[40] Luisada,[35,36] Minhas and Gasul[36]).

The conclusions are based partly on hypothetical grounds, clinical observations, and experimental facts. The reported data fall into two groups: (1) temporal relationship between the sounds recorded in the extracardiac or intracardiac phonocardiograms and other cardiac events, i.e., events in the cardiac chambers or the great vessels which are recorded in electrocardiograms, electrokymograms, pulse tracings, or pressure measurements (but the coincidence of two events does not prove their causal connection and therefore may be misleading); (2) correlations between the site of maximum intensity of the different components of the first heart sound and the location of the sound-producing structures.

In our study we tried to approach the problem by measuring (1) the *intensity distribution* (and distance) of the two main components of the split first heart sound at five different points on the precordium (2 RIS, 2 LIS, 3 LIS, 4 LIS, apex) in a statistical analysis of data from children who were 2 to 12 years of age and (2) the *intensity variations* of the aforementioned vibrations under functionally altered conditions, i.e., respiration and Valsalva maneuvers.

Method and material

Simultaneous electrocardiograms and phonocardiograms were recorded by means of an Atlas four-channel oscillograph on photosensitive paper using the Maass and Weber method[31,57] which operates with 5 different high-pass filters. The nominal frequencies and the slope of attenuation are as follows: t = 35 c.p.s., 7.5 decibel per octave; m_1 = 70 c.p.s., 18 db./octave

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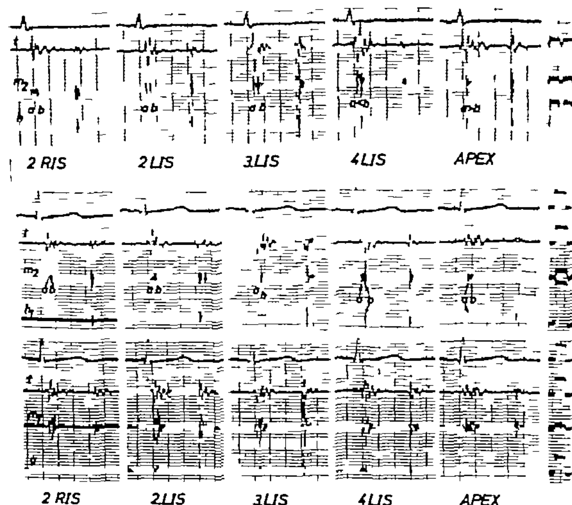


Fig 1 Representative electrocardiograms and phonocardiograms from two children which show the typical intensity distribution of the two main components (a, b) of the physiologically split first heart sound in different frequency band and at five locations (see under Method) Above Fifteen year-old girl Same case as in Fig 4 Below Ten year-old girl whole frequency range (l low m medium low m medium high h high g earlike) Distance between the heavy vertical lines = 0 1 second On the right calibration by means of the 1 millivolt ECG signal.

m = 140 c p s 24 db/octave h = 250 c p s 24 db/octave g = earlike = 140 c p s 12 db/octave

A Investigations on intensity distribution In the first part of the investigation we took 60 tracings out of a material consisting of some 2 000 phonocardiograms all of which were recorded (1) in five frequency bands (2) at five different locations (2 RIS 2 LIS 3 LIS 4 LIS and apex) (3) at a paper speed of 100 mm per second and (4) with the subject in the recumbent position (for example see Fig 1) The selection was arbitrary with the exception that pathologic cases with systolic clicks were excluded

The recordings were made with constant sensitivity at the five different locations in each individual case but the amplification was adapted to the varying intensity of heart sounds in the five frequency bands in each child The amplification of the four channels was calibrated by means of the 1 millivolt (mv) ECG signal Therefore the amplitudes of the vibrations could be expressed in relative values (mv) thus allowing an interindividual comparison within each frequency range The intensi

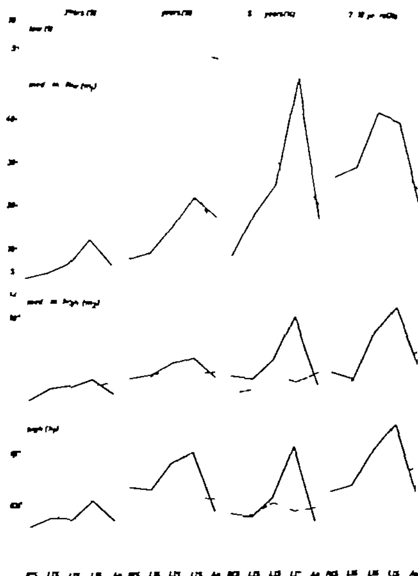


Fig. 2. Graphic representation of the average amplitudes of the first (– – –) and second (——) main components of the split first heart sound in the different age groups, frequency bands, and areas of recording (abscissa). Numbers in parentheses after age show the number of cases.

relations between the five frequency bands could not be established. At all locations and frequency bands where splitting was obvious at least five consecutive amplitudes of the vibrations under discussion were measured in millimeters (mm.) and the means values were taken for further analysis.

The material was first divided into five groups on the basis of age of the subject but the two groups of older children were then put together because there was no evidence of age differences. The final distribution is as follows: 2-3 years of age, 9 cases; 4 years, 11 cases; 5-6 years, 14 cases; 12 years, 26 cases. Within each age group the means of both components of the split first heart sound were evaluated for each location and frequency band. Although the amplitudes of all heart sound were measured, this paper deals only with the complex of the first heart sound. The full results will be published elsewhere.

In addition to the amplitudes, the time of onset of the two major components of the first heart sound in respect to the beginning of the electrocardiogram (the Q wave) was measured. The following abbreviations are used: SI, First heart

sound complex AIa Amplitude of the first major component of SI AIb Amplitude of the second main component of SI Q Ia Interval between the Q wave of the ECG and the beginning of the first component of SI Q Ib Interval between the Q wave of the ECG and the beginning of the second component of SI Ia Ib Individual time difference between the two main components of SI

B Respiration experiments In some children with clearly split first sounds continuous recordings of the medium frequency and high frequency phonocardiogram were made simultaneously with the pneumogram the electrical transformed spirogram or records of the esophageal pressure for at least 1 to 1½ minutes (about 100 to 150 consecutive heart cycles) during quiet respiration As already pointed out by Dornhorst and Leathart the pneumograms correlate well with the spirograms and are therefore a useful reference of the frequency phase and depth of respiration

The consecutive respiratory cycles were plotted one upon the other by setting the maximum inspiratory amplitudes of the respiratory records at 100 per cent When this is done heart sounds occur in all parts of the respiratory cycle allowing a continuous band to be drawn from the amplitudes of the first as well as from the second component of the split first heart sound that reflects the different respiratory variations of these components

C Valsalva maneuvers The straining procedure was performed with the subject in the recumbent position blowing against a mercury manometer which was connected in parallel with the Statham strain gauge or against the closed glottis and the intra esophageal pressure was recorded with the Statham transducer Pressures of from 20 to 60 mm Hg were held for 10 to 20 seconds The maneuver which we often use as an aid in the differentiation between left sided and right sided murmurs (according to Zinsser and Kay[47]) can be performed with some patience in most children over 4 years of age

The pressure curves were recorded synchronously with the heart sound in different frequency bands by means of the above described apparatus using a paper speed

Table I

Age	N	x ± SE	S D	Difference	S	Dif /SD	p
QI							
3	47	48 1 ± 0 55	3 7				
4	58	53 1 ± 0 72	5 5	5 0	0 96	5 2	< 000001
5–6	80	52 5 ± 0 58	5 2	−0 6	0 92	0 6	< 55
7 12	192	55 2 ± 0 55	7 0	2 7	0 5	5 4	< 000001
2 12	377	53 4 ± 0 33	6 4				
QIb							
2 3	40	66 8 ± 1 12	7 1				
4	57	72 1 ± 0 83	6 2	5 3	1 13	4 6	< 00001
5–6	77	74 5 ± 0 57	5 2	2 4	0 97	5	< 02
7 12	163	78 6 ± 0 63	7 7	4 1	0 83	4 9	< 000001
2 12	337	75 2 ± 0 42	7 8				
Ia–Ib							
2 3	39	18 8 ± 0 88	5 5				
4	52	18 9 ± 0 47	3 4	2 7	0 59	4 6	< 00001
5–6	72	1 (± 0 34	9	1 3	1 0	1 3	< 2
7 12	153	22 9 ± 0 79	3 7				
2 12	316	21 5 ± 0 3	4 1				

Difference between values.

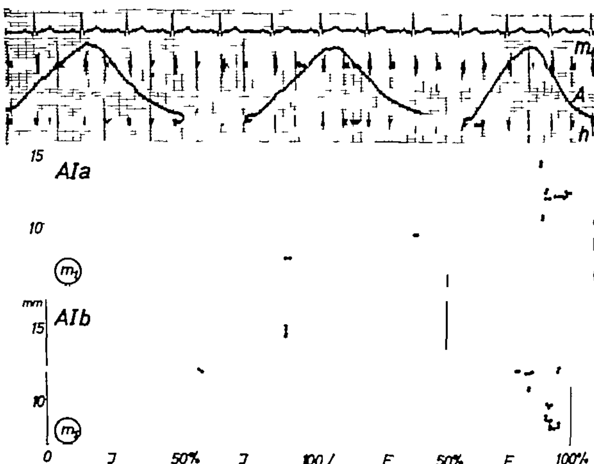


Fig. 3. *Above:* Part of the original recording which shows the ECG, phonocardiogram, and pneumogram taken from a 6-year-old boy. Distance between the heavy vertical lines = 0.1 second. *Below:* Graphic evaluation of the amplitudes (given in millimeters) of the first (*AIa*) and second (*AIb*) components of the split SI (ordinate) against the phase of respiration in per cent of maximum inspiration or expiration (= 100 per cent) according to the principles described in the section on *Method*. *I*, Inspiration; *E*, Expiration.

of 100 mm. per second. Special attention was paid to Phases III and IV according to Hamilton and associates.[1]

Results

A. The intensity distribution of the two major components of the first heart sound along the anterior chest wall is represented in Fig. 2. The average amplitudes *of the two components are plotted* in relative terms (millivolts) on the ordinate versus the area of recording for each frequency band and age group. In the low frequency band the differentiation between the two components of the first sound has not been tried, although it is often possible to separate right sided and left sided events in this tracing.

1. As can be seen, there is a general tendency for all measured components to *increase with age* if comparable values (same frequency band and area) are considered. At least this holds for the points of maximum intensity.

2. The *points of maximum intensity* are in nearly all instances different for both components of the first heart sound. Whereas the second component (AIb) has *with one exception its greatest amplitude* at the fourth left intercostal space, the behavior of the first group of vibrations is different. In the medium high frequency and high frequency bands there is a fairly uniform pattern. The lowest values are at the second right intercostal space. They show a gradual increase along the left sternal border, reaching their maximum at the apex. In the medium low *frequency*

band the point of maximum intensity is at the third or fourth intercostal space thus reflecting the behavior of the maximum amplitudes in the low frequency range

3 The *intensity relations between both components* at different areas are the most interesting point Although the second component (AIb) has the greater intensity along the left sternal border especially in the medium high frequency and high frequency bands (and also in the medium low frequency range of the older children those 5 to 12 years of age) the relationship changes at the apex Here the first component of the split SI predominates This observation already described in adults by Leatham[7] is therefore *a constant feature in all of the children included in this study*

4 The *average time interval* from the beginning of the Q wave to the onset of the first and second components of the split first sound in the various age groups and the average distance between both components calculated from the individual time difference (Ia Ib) are given in Table I The average values within the whole group are 53 4 ± 0 3 msec (S D 6 4) for the first component and 75 2 ± 0 42 msec (S D 7 8) for the second component of the first heart sound As can be seen these values show a tendency to increase with age a finding which is significant in most instances The average splitting interval is 21 5 ± 0 2 msec (S D 4 1) The differences between the younger children (2-4 years) and the older children (5 12 years) are also significant ($p < 001$)

B The respiratory variations of the amplitudes of both components of the split first heart sounds in two typical patterns are illustrated in Figs 3 and 4 The upper part of each illustration shows a section from the original phonocardiograms which are evaluated below according to the principles described under *Method*

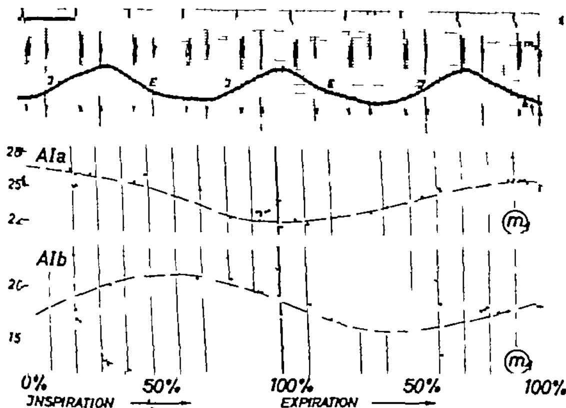


Fig 4 Respiratory variations of both components of split SI Method of representation is the same as that in Fig 3 Same girl as in upper section of Fig 1 The amplitude of AIb reaches its peak during inspiration somewhat earlier than in Fig 3 Inspiratory decrease in intensity of AIa as in Fig 3 *I* Inspiration *E* Expiration

A

B

C

20 mm Hg

Fig. 5 Three examples which show the electrocardiogram, phonocardiogram, and oral pressure curve at the end of (1) t after the training procedure. In the early post training period the initial component of the first sound complex ( ) is small where the second component (b) predominates. With the following heart cycles the first component tends to increase whereas the second component decreases so that the amplitude relation changes. E and L indicate respectively the early (1) to post-training first sound complexes which are segmented photographically and put one below the other. Fig. 6 the electrocardiogram (black lines) time reference.

The striking feature is the different behavior of the *two components* of the split first sound during the phases of respiration. Whereas the initial component (AIa) decreases in intensity during inspiration, the second group of vibrations shows in the first case much greater variations but the intensity rises averagewise during inspiration and falls during the second part of expiration. In the second case, which is the same as in the upper part of Fig. 1, the intensity of the second component (AIb) reaches its peak somewhat earlier during *inspiration* and decreases at the beginning of the expiratory phase. As established elsewhere, this behavior cannot be explained by extracardiac factors such as varying interposition of lung tissue, *although respiratory modifications in the* conduction of sound may interfere with changes in the generation of sound.[11] These conclusions are based mainly on the fact that the variations of those factors which influence the conduction of sound—such as lung volume and tension, intrathoracic pressure, displacement of the heart and diaphragm—are not in phase with the changes in intensity of heart sound.

The temporal shifting of both components during respiration is difficult to measure exactly and is therefore outside the scope of this publication. In lower degrees of splitting both components tend to merge, particularly in the inspiratory phase.

C. Three typical Valsalva experiments are represented in Fig. 5, which is limited to the poststraining Phases III and IV. Immediately after the intrathoracic pressure falls, both heart sounds are still faint as in the pressure phase. Then the first component of the split first heart sound, including the initial group of the low frequency tracing still visible at the end of Phase II, diminishes or sometimes disappears in the early poststraining period (Phase III).

In contrast, the second main component of the split SI rises rapidly after the

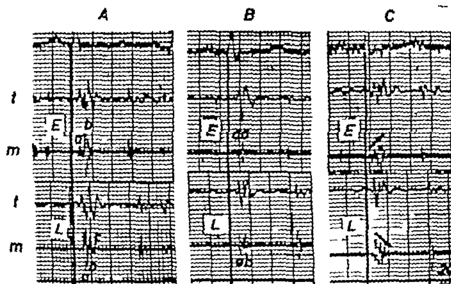


Fig. 6. Three early (*E*) and three la (*L*) heart sound complexes h ch dicated in Fig. 5 (*A*, *B*, *C*) and plotted one below he other using the ECG (black lines) me reference. The changes f both components of the split SI are obvious, especially in the medium frequency band (*m*). I I there d stinct reversal in he relation hip of the amplitudes bet een od *b*. Besides th th rd vascul component of SI ( ) ppears in the late heart cycle. I *B* both components are nearly equal in the late po t training period hereas the initial component dominates in the early sound complex. In *C* the ea h post training first sound complex show cre- scendo and the lat complex decrescendo-l ke pattern. Note also th hift of the second heart sound in the post training phase nd the dela ed ppearance of marked third sound in I

A

B

C

20 mm Hg

Fig. 5. Three examples which show the electrocardiogram, phonocardiogram and oral pressure curves at the end of and just after the training procedure. In the early posttraining period the initial component of the first sound complex ( ) is seen. B whereas the second component (b) predominates later. With the following heart cycles the first component tends to increase whereas the second component decreases so that the amplitude relation hip changes. E and L indicate respectively the early and late posttraining first sound complexes which are augmented photographically and put one below the other in Fig. 6 using the electrocardiogram (black line) as time reference.

ventricle (Feruglio[1,11] Luisada and associates[7])

The other main component of the split first heart sound (1) has its point of maximum intensity at the lower sternal edge where it has regularly a greater amplitude than the first component (2) increases in intensity during inspiration and (3) reaches its maximum amplitude immediately after the release of pressure in the Valsalva maneuver. This is normally the second main group of vibrations within the first heart sound complex. Its average time of appearance is 75 msec after the onset of the Q wave of the ECG

When these results are confronted by the contradictory theories of aortic or tricuspid origin of these vibrations the facts strongly favor the concept of tricuspid origin. The intensity distribution at the thoracic wall is not that which could be expected from a sound originating in the aorta. Also the amplitude of the sound due to closure of the aortic valve not demonstrated here has another intensity distribution in the same material

In contrast the increasing amplitude downward to the lower sternal edge corresponds with the premises which should be fulfilled by a sound originating from the tricuspid valve. The early increase in intensity during the inspiratory and post straining periods is further evidence for the right sided genesis of the second main component of the normally split first heart sound. It can reasonably be related to the augmented venous return to the right heart which is due mainly to thoracic aspiration or is the consequence of the pooling of venous blood during the pressure phase of the Valsalva maneuver. An aortic ejection sound would be expected to have another intensity distribution and to show variations with respiration and the straining procedure which resemble the left sided hemodynamic changes but not to behave in the opposite way

Furthermore the temporal relationships between the second main group of vibrations and the electrocardiogram are in the same range (75 ± 0.42 msec S D 7 8 msec) as the values reported (1) for the delay of the first sound vibrations recorded within the right heart (Moscovitz and associates[14] Feruglio[11]) and (2) for the rapid rise in right ventricular pressure or closure of the tricuspid valve (Coblentz and associates[5])

Finally the time difference between both main vibrations of the split SI (21.5 ± 0.2 msec S D 4 msec) means that in about 95 per cent of the cases investigated the splitting interval ranges from 13 5 to 29 5 msec which is compatible with the measured values for the normal asynchronism of right sided and left sided dynamic events in animals and men (Katz[15] Laurt and Muller[16] Braunwald and associates Sumet and associates[17] Gribbe and associates[18]) This interval is too short to represent the isometric contraction phase of the left ventricle which lasts about 50 msec (Wiggers[19] Braunwald and associates[1] Luisada and associates)

If the complex of the first heart sound consists of three distinct groups of vibrations (which is not a rare finding in our material) that component which has according to its intensity distribution timing respiratory and straining variations the characteristics of the sound due to closure of the tricuspid valve is the second group of vibrations and is followed by a third one which has the qualities of a vascular or ejection sound. This third group of vibrations appears about 50 msec after the initial component of the first heart sound

So there is no doubt that at least in the age group under study (2 to 12 years) the second main component of the normally split first heart sound is of right sided (tricuspid) origin. The normal splitting of SI is due therefore to asynchronous closure of the atrioventricular valves or to the time difference between rapid rise in pressure in the two heart chambers

Summary

1 The intensity distribution along the anterior chest wall timing respiratory and poststraining variations of the physiologically split first heart sound especially in the medium high frequency range has been investigated by means of multiple filter phonocardiography in children who were 2 to 12 years of age

2 In 60 children from 2 to 12 years of age the first main component of the split first heart sound has on an average its maximum intensity at the apex wh

intrathoracic pressure relaxes This results sometimes in a (pseudo) delayed onset of SI With the following heart beats a gradual rise in the initial component (AIa) is associated with a decrease in AIb which reaches its maximum amplitude during the first two or three poststraining beats Therefore after a few beats the initial intensity relation between both main vibratory groups of SI reverses

In Fig 6 one early (*E*) and one late (*L*) poststraining first heart sound complex from the same Valsalva experiments illustrated in Fig 5 are plotted one below the other with the ECG used as time reference As can be seen there are always the above mentioned changes in intensity which lead (1) to a reversal of the amplitude relation between both components of the split first heart sound if the splitting is distinct and the first component (AIa) is normally predominant at the area of recording (Fig 6 *A*) (2) to a relative increase of the first component in respect to the second only whereby the second component remains equal or predominant in the post straining period if the second component is normally overwhelming at the area of recording i e 4 ICS (Fig 6 *B*) or (3) to a crescendo like pattern of the first sound complex in the early poststraining period which changes to a decrescendo like pattern some beats later if the splitting is not quite distinct (as is often the case in the medium low frequency band) (Fig 6 *C*)

Without regard to the afore mentioned differences the individual pattern can always be reproduced with a high degree of accuracy under similar conditions

Variations of the described typical pattern are the consequence of (1) different duration and intensity of the straining procedure (2) variable filling of the low pressure system anterior to the left and right heart (congestive failure) (3) variable duration of circulation time in the lung (4) the degree of reflex vasomotor activity in the systemic (and lung?) circulations

Hence the reactions to the Valsalva experiment which are recorded in the phonocardiogram depend on the same factors which influence the hemodynamic response to the straining procedure (Burger and Michel[4] Elisberg and associates[6,7] Gorlin and associates[12] Hamilton and associates[14] Howard and associates[17] Knowles and associates[18] Lee and associates[19] Rushmer[20] Sharpey Shafer[21]

The changes in intensity and timing of both components of the *second heart sound* are outside the scope of this article and are described in detail elsewhere (Heintzen[16])

The *third heart sound* reaches its maximum amplitude during the late poststraining period (Phase IV) which is in accordance with its supposed left sided origin This is of interest in so far as the first component of the split SI attains its crest just after the third sound (Figs 5 *A* and 6 *A*)

Conclusions

To summarize our findings there is one component of the normally split first heart sound (AIa) which (1) has its point of maximum intensity in the medium frequency and high frequency bands at the apex where it is greater than the other component (2) decreases in amplitude with inspiration and (3) reaches its maximum sometimes overshooting it in the late poststraining period of the Valsalva maneuver This is usually the first component of the normally split first heart sound It appears about 50 msec after the Q wave of the electrocardiogram

All of these facts are quite in accordance with the concept that the initial vibrations of the first heart sound have their origin on the left side of the heart and the medium high frequency fraction is related to closure of the mitral valve for the following reasons (1) The intensity distribution is identical with that of other vibrations of known left sided (mitral) origin (2) The decrease in amplitude with respiration reflects the inspiratory diminution of blood flow to and through the left heart (3) The late poststraining intensity crest is the consequence of the delayed appearance in the left heart of that blood wave which was accumulated in the venous system during the elevation of intrathoracic pressure

Finally the time of onset of the vibrations under discussion coincides with the reversal of the left sided atrioventricular pressure differential (Braunwald and associates[3] Luisada[23,24]) and with the first sound vibrations recorded within the left

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The indications for measurement of left heart pressures in mitral and aortic valvular disease

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The assessment of obstruction of the mitral and aortic valves relies on measurement of the transvalvular pressure gradient and simultaneous estimation of the cardiac output. Evaluation is difficult in the presence of mitral or aortic regurgitation because the forward flow across the valve in these circumstances is greater than expected from the cardiac output. The severity of mitral or aortic incompetence may be assessed from the clinical, electrocardiographic, or radiologic evidence of increased left ventricular stroke volume, and additional information is provided by the left atrial or aortic pressure pulses. Regurgitant flow can also be estimated by indicator-dilution methods[1-3] or angiocardiography.[4-6]

An appreciable risk is involved in attempts to measure left heart pressures, and the value of the data obtained must be considered in relation to the morbidity of the procedure. In many situations the information provided by right heart catheterization is adequate. The indications for measurement of left heart pressures are clarified in this report of 133 consecutive cases of mitral or aortic valvular disease which were studied in the past year.

Methods

The techniques used are described in detail elsewhere.[6] Aortic pressure was recorded continuously using the Seldinger method,[7] and right heart catheterization was performed in each case. Left atrial pressures were obtained via a slotted bronchoscope which was then removed, leaving the needle in place.[8] Left ventricular pressures were recorded by direct puncture through the anterior chest wall[9] or by retrograde catheterization using a Cournand catheter through the right brachial artery. When conditions were constant, pressures were recorded simultaneously on each side of the mitral (Fig. 1) or aortic (Fig. 2) valves, and cardiac output was estimated by the Fick method. The middle of the chest at the level of the second costal cartilage was taken as the base line for pressure measurements. P23Db strain gauges and a four-channel direct-writing Sanborn Poly-Viso were used to record the pressures, which were then replotted on the same scale (Figs. 1, 2, and 3). The content of oxygen in the blood was determined by the Van Slyke method.[11]

The areas of the valves were calculated by using standard orifice formulae[12] on the

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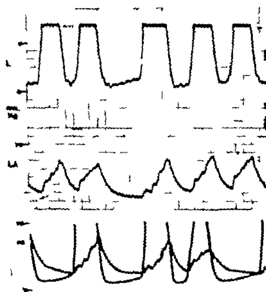


Fig 1 Direct measurement of the left atrial and left ventricular pressures in mitral stenosis and incompetence

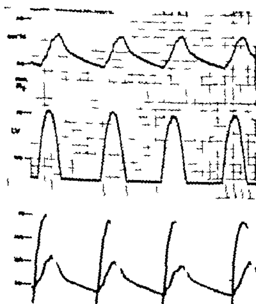


Fig 2 Direct measurement of the aortic and left ventricular pressures in aortic stenosis

assumption that no regurgitation was present Cardiac output valvular areas and pulmonary vascular resistance were expressed in relation to body surface area so as to minimize the effects of differences in body size The Ry/v ratio[18] was calculated from the left atrial pressure pulse adjusted to a base line at the level of the sternal angle Measurements of the aortic tidal peak time were corrected for variations in heart rate by dividing by the square root of the cycle length in seconds The frontal area of the left atrium was measured with a planimeter on overpenetrating posterior anterior radiographs taken at standard distance

Results

A Mitral stenosis (*Table I*) Sixty nine patients with predominant mitral stenosis were studied Some had soft basal murmurs but there was no other evidence of aortic valvular disease Thirteen additional patients had aortic valvular lesions of considerable degree There was clinical evidence of slight or moderate mitral insufficiency in two thirds of the patients

Measurements of left heart pressure were necessary in half of the patients with pulmonary vascular disease or with lesions of critical severity i e cases in which there was doubt as to the need for operation On the other hand studies of the left heart were rarely required for the assessment of severe uncomplicated mitral stenosis or in patients with trivial disease e g after successful commissurotomy The left ventricu

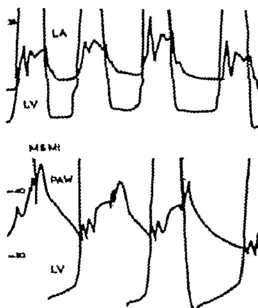


Fig 3 Superimposed left atrial (*above*) or pulmonary arterial wedged (*below*) and left ventricular diastolic pressures in two patients with combined mitral stenosis and incompetence

*Table I Eighty two patients with predominant mitral stenosis**

	Total number	Number with MI	Left heart pressure measured: LA	Left heart pressure measured: LV	Calculated mitral valvular area (cm/M)	LV mean diastolic pressure (mm Hg)	Ry/r: Pure MS	Ry/r: MS with MI	Cardiac index (L/min/M)
PVR more than 10 units per sq meter	9	3	3	3	0.3	13	1.5	1.9	1.8
PVR 5 to 10 units per sq meter	14	11	7	8	0.5	11	0.9	1.1	2.0
Severe uncomplicated MS	8	0	0	1	0.5	10	—	—	2.6
Severe MS with MI	10	10	3	8	0.4	9	—	1.7	2.3
MS of critical severity	14	8	4	7	0.8	9	0.9	1.7	2.6
MS with aortic valvular disease	13	5	3	12	0.9	11	1.1	—	2.6
Trivial MS	14	9	1	2	1.1	11	—	1.0	3.0

*For detailed analysis these patients were divided into seven groups ranging from severe to trivial stenosis. Patients with an increased pulmonary vascular resistance (PVR) form the first two groups. Cases of severe mitral stenosis (MS) with mitral incompetence (MI) were separated from the uncomplicated cases for comparative purposes. In the patients with considerable aortic valvular disease the mitral stenosis was only moderately severe. Areas of the mitral valve were calculated from the hemodynamic data on the assumption that no regurgitation was present. Valvular area, pulmonary vascular resistance, and cardiac output are expressed in terms of body surface area (per square meter). Ry/r ratio was measured from left atrial pressure records.

*Table II Twenty five patients with predominant mitral incompetence**

	Total number	Left heart pressure measured: LA	Left heart pressure measured: LV	LV mean diastolic pressure (mm Hg)	Ry/r	Cardiac index (L/min/M)
PVR more than 5 units per sq meter	4	3	3	18	6	2.1
Severe uncomplicated MI	4	2	3	11	6	1.9
MI of critical severity	4	3	3	10	5	2.8
Trivial MI	8	1	1	16	—	2.9
MI with significant AI	5	0	5	13	—	2.7

*These patients are divided into five groups ranging from severe to trivial incompetence. Patients with an increased pulmonary vascular resistance (PVR) form the first group. The last group in this table consists of patients with both aortic (AI) and mitral (MI) incompetence.

lar mean diastolic pressure was measured in 29 patients without aortic valvular disease and averaged 10 mm Hg (range 4 to 16 mm Hg). In the patients with serious aortic valvular disease the mitral stenosis was only moderately severe. Measurements of left ventricular pressure were obtained in these cases primarily for evaluation of the aortic lesion.

B Mitral incompetence (Table II). Twenty five patients with predominant mitral insufficiency were studied. In 5 there was also significant aortic incompetence. The lesion was regarded as of critical severity in patients with signs of considerable left ventricular enlargement but few symptoms; the cardiac output was normal in this group. Measurements of pressure in the left heart were obtained in three quarters of the patients with severe mitral incompetence but in only one quarter of those judged on the basis of absence of left ventricular hypertrophy to have *trivial* lesions. The left ventricular mean diastolic pressure was measured in 10 patients with isolated mitral insufficiency. In the uncomplicated cases the average value was 11 mm Hg (range 6 to 16 mm Hg).

*Table III Left atrial pressure pulse in 30 patients with mitral valvular disease**

	Pure MS	MS and MI	Pure MI
Number of cases	7	14	9
Cardiac index (L /min /M²)	2 1	2 1	2 4
Frontal LA area (cm²)	66	79	71
LA pulse pressure (v-y) (mm Hg)	12	14	27
R_1/ ratio	1 2	1 7	5 6

*The average findings in the left atrial (LA) pressure pulse compared in patients with pure mitral stenosis, mitral stenosis complicated by mild to moderate incompetence (MS + MI) and pure mitral incompetence

Records of left atrial pressure were available in 30 patients with mitral valvular disease (Table III) The size of the left atrium as judged from the posteroanterior radiograph and the cardiac index were similar in patients with stenotic, incompetent and combined lesions High Rv v ratios were found only in the group with pure mitral incompetence

C Aortic valvular disease (Table IV) Twenty six patients with isolated aortic valvular disease and 18 patients with combinations of aortic and mitral lesions were studied The severity of the aortic stenosis varied greatly Four patients had minor lesions and in 5 more classed as critical there was doubt as to the need for operation

Left ventricular pressures were obtained in all but 2 of the patients with aortic valvular disease The left ventricular mean diastolic pressure ranged from 5 to 35 mm Hg Measurements of aortic pressure were available in all cases There was a tendency to a slower upstroke in patients with left ventricular failure and a more rapid upstroke in those with mild lesions The timing of the aortic tidal peak could not be related to the severity of the stenosis

Discussion

Measurement of the diastolic pressure gradient across the mitral valve requires estimation of both left atrial and left ventricular pressures It is generally agreed that the mean pulmonary arterial wedged pressure is a good index of the mean left atrial pressure but the wave form may be considerably damped in transmission to the wedged catheter[1] However the simplicity of the wedged technique and the small risk entailed make it preferable when the information it gives is adequate The error produced by using the mean wedged pressure as an estimate of left atrial pressure is small when the gradient is large (Fig 3 *below*)

The mean left ventricular diastolic pressure in mitral stenosis averaged 10 mm Hg

*Table IV Forty four patients with aortic valvular disease**

	Total number	Calculated aortic valvular area (cm²/M²)	LV mean diastolic press (mm Hg)	Cardiac index (L /min /M²)	Aortic pulse: Maximum upstroke (mm Hg/)	Aortic pulse: Corrected tidal peak (sec)
AS with LV failure	4	0 25	28	2 3	380	0 29
Severe uncomplicated AS	9	0 3	11	2 3	770	0 4
Severe AS with AI	4	0 4	2	2 6	680	0 28
AS of critical severity	5	0 5	12	3 1	570	0 25
Mild uncomplicated AS	4	0 7	13	3 4	950	0 28
Severe AS with MS	4	0 3	9	2 1	5 0	0 27
Severe AS with AI and MS	5	0 4	13	2 7	1 100	0 24
Severe AI and MS or MI	9	—	11	2 8	1 470	0 19

*These patients are divided into five groups of isolated aortic valvular disease [illegible] severe to mild [illegible] and three groups of [illegible] mitral lesions [illegible] The first group had left ventricular failure at the time of study [illegible] patient with [illegible] complicated [illegible] with cases [illegible] Aortic valvular area was calculated from the hemodynamic data [illegible] that no regurgitation [illegible] in terms of body surface area (per square meter)

in this study with considerable individual variation and similar findings have been reported by others.[8] The use of an arbitrary value of 5 mm. Hg will lead to considerable error in the calculation of the mitral valvular area if the gradient is small. If the wedged pressure is high and there is no associated abnormality which might raise the left ventricular diastolic pressure, such as aortic valvular disease or mitral incompetence, a value for the left ventricular diastolic pressure may be assumed without serious error. If the cardiac output is normal, a low wedged pressure indicates a mild lesion. In other circumstances, for instance, moderate elevation of the wedged pressure, evidence of left ventricular disease, or a low wedged pressure with restriction of the cardiac output, left ventricular pressures are needed for accurate assessment of the stenosis. Left atrial pressures are required only if a small gradient must be measured precisely because the cardiac output is low, as in patients with pulmonary vascular obstruction or tricuspid valvular disease.

In predominant mitral incompetence the left atrial pressure may appear to show diastasis when in fact a considerable gradient persists (Fig. 3, *above*). Measurement of left ventricular pressure is probably necessary unless the wedged pressure falls to normal levels at the end of diastole. Left atrial puncture is needed to measure a small gradient accurately, but is rarely of practical value because a small gradient may be found in mitral incompetence without significant stenosis.[17]

The left atrial v wave in mitral valvular disease is related to the regurgitant flow but is also influenced by the systolic inflow from the pulmonary veins and by the volume and mechanical properties of the left atrium.[18] The Ry/v ratio has the advantage of taking into consideration the increasing rigidity of the left atrial wall as the chamber is distended.[12] However, the effects of mitral regurgitation on the left atrial pressure pulse cannot be distinguished with certainty if a mitral gradient persists throughout diastole.[6] Variations in left atrial volume and cardiac output are relatively small (Table III), and it seems likely that differences in the elasticity of the left atrial wall are mainly responsible for this difficulty.

The character of ventricular ejection and the effects of aortic regurgitation determine the form of the aortic pressure pulse, but the physical properties of the aorta and the timing of flow to the peripheral vessel[11] also play a part. The separation of these factors is difficult, and in the present study the maximum rate of rise in pressure and the corrected tidal peak time did not distinguish aortic stenosis from stenosis with moderate insufficiency. A prominent anacrotic wave in aortic stenosis may produce a rapid upstroke, and a large stroke volume may lead to a sustained pulse with only a moderate degree of stenosis. Left ventricular and aortic pressures (Fig. 2) are needed to estimate the severity of aortic stenosis accurately, but the use of peripheral arterial pressures produces little error if the gradient is large.

Conclusions

Measurements of left ventricular pressure are necessary for the precise assessment of mitral valvular disease when there are lesions producing left ventricular hypertrophy or restricting the cardiac output, or when the pulmonary arterial wedged pressure is only moderately elevated. When the difference between mean wedged and left ventricular diastolic pressures is small, left atrial puncture is needed to measure the gradient accurately. Direct left atrial pressures are rarely of value in assessing mitral incompetence.

In aortic stenosis, left ventricular pressures are needed if there is doubt as to the severity of the obstruction.

Summary

The indications for direct measurement of left atrial and left ventricular pressure are analyzed in the light of experience with 133 cases of mitral or aortic valvular disease. Left ventricular pressures are more often needed than direct left atrial pressures because the pulmonary arterial wedged pressure frequently gives adequate information without the risks of left atrial puncture.

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Pulmonary venoarterial shunting in hepatic cirrhosis

Including a case with cirsoid aneurysm of the thoracic wall

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The association of peripheral cyanosis, clubbing of the digits, and liver disease was first recognized in 1884 by Fluckiger. Gilbert and Fournier made similar observations in children with this disease in the absence of overt pulmonary disease. Keys and Snell[3] ascribed the cause of the arterial desaturation in patients with cirrhosis of the liver to a shift of the oxyhemoglobin dissociation curve to the right. Subsequently, Wilson and co-workers[4] demonstrated the existence of a moderate degree of pulmonary venoarterial admixture in their 10 patients with cirrhosis of the liver.

Cutaneous vascular lesions are commonly observed in patients with cirrhosis of the liver.[5] The cause of such lesions is unknown, but they have tentatively been attributed to an elevated level of circulating estrogen and not to arterial desaturation. Thus the mechanism of reduced arterial oxygen saturation in patients with cirrhosis of the liver remains partially unclear, as does the possible relation of this change to other vascular disturbances noted in this disease.

The purpose of this study was to examine alveolar-arterial gas exchange so as to estimate the degree of venoarterial admixture present in 15 patients with cirrhosis of the liver. The development of a cirsoid aneurysm of the thoracic wall in a 57-year-old man with Laennec's cirrhosis, who was studied over a period of several years, is reported in detail.

Materials and methods

Fifteen patients, 13 men and 2 women, with cirrhosis of the liver were studied while they were resting in the supine position, breathing first ambient air and then 100 per cent oxygen. The ages of these patients ranged between 16 and 63 years (average 47.3 years). The duration of their illnesses ranged between 2 and 9 years. Twelve patients had Laennec's cirrhosis of the liver, 1 patient (Case 14) had juvenile cirrhosis, and in another patient (Case 12) cirrhosis was thought to be secondary to repeated exposure to various chemical toxins. In all, the diagnosis was made on clinical and laboratory grounds and verified either by needle biopsy of the liver or at autopsy.

Arterial oxygen and carbon dioxide contents were determined by the method of Van Slyke and Neill. Expired oxygen and carbon dioxide concentrations were determined by the Beckman L-2 and Liston-Becker analyzers, respectively. Arterial

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Table I Gaseous exchange in patients with cirrhosis of the liver on breathing room air

Case	Arterial oxygen saturation ( )	Arterial oxygen tension (mm Hg)	Arterial carbon-dioxide tension (mm Hg)	Alveolar-arterial oxygen tension gradient (mm Hg)
1	90	71	37	38
	94	8	36	34
3	93	71	36	41
4	94	8	38	25
5	93	85	37	24
6	81	65	41	45
7	9	7	27	31
8	93	79	28	32
9	80	45	40	58
10	89	59	36	46
11a	86	5	29	63
11b	91	61	31	41
1	90	5	47	46
13a	8	41	31	75
14	89	60	32	56
15	94	80	31	37
Range	78–94	41–88	27–47	24–75
Mean ± S D	89 ± 9 7	67 ± 13	34 8 ± 5 3	43 ± 16
Normal	94 4 ± 2 6	85 0 ± 13	39 0 ± 4 0	13 0 ± 6 5

blood pH was determined by the Beckman GS pH meter The carbon dioxide tension of the arterial blood was obtained from the Singer Hastings nomogram using the whole blood arterial carbon dioxide content and pH The arterial oxygen tension (Pao) was determined polarographically from whole blood by a method employing the Clark electrode The alveolar oxygen tension (PAo) was calculated from the alveolar air equation The difference between the alveolar oxygen tension and the arterial oxygen tension is the A a gradient Under the conditions of these experiments the A a gradient in normal individuals when they are breathing room air is 13 ± 6 5 mm of mercury

After the ambient air studies were completed the patients breathed pure oxygen for at least 30 minutes This allows sufficient time to complete nitrogen washout from all alveolar spaces resulting in virtually complete equilibrium between the alveolar air and pulmonary capillary blood Under these circumstances an alveolar arterial (A a) oxygen tension gradient of less than 60 mm of mercury is observed in normal individuals in the supine position thus indicating the presence of a small degree of venoarterial admixture even in normal subjects A larger A a oxygen tension gradient is diagnostic of abnormal pulmonary venoarterial admixture The magnitude of this shunt can be estimated from the following equation

$$\% \text{ shunt} = 100\left(1 - \frac{AV \text{ }O_2 \text{ diff}}{AV \text{ } O_2 \text{ diff} + G}\right)$$

where G represents the A a oxygen tension gradient multiplied by (0 003) the Bunsen solubility factor for oxygen at 37 5 C expressed as milliliters per millimeter of mercury Utilizing this equation and assuming an oxygen difference of 4 3 volumes per cent between the systemic and the pulmonary arteries we estimated the fraction of the cardiac output represented by the venoarterial shunt in each patient The assumption of an arterial mixed venous oxygen content difference of 4 3 volumes per cent is permissible because extreme variations in this factor make only small differences in the estimated shunt

Results

When they were breathing room air a majority of the patients had a moderate degree of arterial oxygen desaturation as illustrated in Table I The mean arterial saturation for the group was 89

Table II Pulmonary venoarterial admixture in patients with cirrhosis of the liver using the 100 per cent oxygen breathing method

Case	Arterial oxygen tension (Pa_{O_2}) (mm Hg)	Arterial carbon-dioxide tension (Pa_{CO_2}) (mm Hg)	A-a oxygen tension gradient (mm Hg)	% Shunt
1	191	37	462	4
	356	25	310	18
3	608	39	60	4
4	483	39	182	11
	06	38	155	10
6	248	41	414	22
7	593	24	64	4
8	237	29	443	24
9	210	37	436	24
10	599	40	63	4
11a	228	36	429	23
11b	209	42	439	23
1	448	50	212	13
13a	199	31	467	25
13b	201	31	465	24
14	90	31	577	29
15	293	30	3 6	21
Range	90–608	24–50	60–577	4–29
Mean ± S D	355 ± 168	3 ± 7	327 ± 168	18 ± 8

per cent and ranged between 78 and 94 per cent The mean alveolar arterial (A a) oxygen tension gradient was 43 mm of mercury and ranged between 24 and 75 mm of mercury

In Table II blood gas findings on 100 per cent oxygen are reported A large alveolar arterial (A a) oxygen tension gradient was found in 12 patients The mean A a oxygen tension gradient for the group was 327 mm of mercury and corresponded to a mean venoarterial admixture of 18 0 per cent of the cardiac output Two cases Cases 11 and 13 were studied on two occasions separated by an interval of several months The degree of venoarterial admixture estimated in the second study did not change from that obtained earlier The mean venoarterial admixture will drop to 17 per cent of the cardiac output if these two values are excluded

Case report

A 57 year-old white man developed ascites and jaundice in July 1948 (Case 13 in Tables I and II) He gave history of excessive alcoholic intake for the previous 30 years His ascites and jaundice gradually subsided after liver therapy and abstinence from alcohol In April 1950 hoarseness exertional dyspnea and cyanosis appeared Numerous spider nevi were observed over the upper extremities and the thorax The liver was moderately enlarged firm and nontender The spleen was not felt A vascular lump the size of a quarter of dollar appeared in the left lower posterior axillary region, and systolic murmur was heard over it There was no history of previous trauma to this site In November of that year he experienced two episodes of hematemesis and melena The bleeding was controlled with the application of a Blakemore tube In 1951 he experienced frequent infections of the upper respiratory tract and clubbing of the fingers and toes was observed for the first time As the vascular lump enlarged cyanosis and dyspnea progressively increased A to-and fro murmur was now heard over the mass The heart had increased moderately in size. There was no evidence of ascites or peripheral edema The tip of the spleen became palpable.

When last seen in February 1954 the patient exhibited definite cyanosis of the face lips and nail bed Clubbing of the fingers and toes was marked The blood pressure was 126/70 mm Hg The neck veins were slightly distended Fine crepitant râles were heard over both lung bases Overlying the tenth rib in the left axillary region there was an irregular nontender partly compressible vascular mass that was roughly 13 cm in diameter and was raised about 4 cm above the chest wall. A group of distended veins was clearly visible at its upper end (Fig 1) A to-and fro murmur was heard over the mass The heart size was enlarged and Grade 2 apical systolic murmur was heard The surface of the liver was not grossly nodular and the

edge was felt 6 cm. below the costal margin The spleen was palpable The distribution of pubic hair was of a female type and axillary hair was sparse The testicles were atrophic Bilateral gynecomastia was evident There was a trace of pretibial edema

The pertinent laboratory findings were the following hemoglobin 16 8 17 5 Gm per 100 ml hematocrit 46-48 per cent normal total leukocyte and differential count normal urinalysis serum proteins 4 9 Gm per cent (albumin 1 7 Gm per cent) cephalin flocculation 4+ thymol turbidity 20 6 3 units Bromsulphalein retention 35-41 per cent in 45 minutes total serum bilirubin 1 6 mg per cent (direct 1 1 mg per cent) total serum cholesterol 18? mg per cent (ester 95 mg per cent) alkaline phosphatase 8 9 Bodansky units The 2 hour urine urobilinogen level varied between 3 3 and 6 6 Ehrlich units The blood urea nitrogen and serum electrolytes were within normal limits

The electrocardiogram revealed nonspecific S-T and T wave changes Cardiac fluoroscopy demonstrated diffuse cardiomegaly The pulmonary arteries were actively pulsating otherwise the pulmonary vasculature was normal Injection of radiopaque material into the vascular mass revealed the flow of the dye into vascular structures which were mainly below the diaphragm (Fig 2) A number of physiologic studies were performed these included pulmonary function tests (Table III) measurements of the oxygen contents of blood withdrawn simultaneously from the brachial artery and the aneurysmal mass and cardiac catheterization (Tables IV and V)

At postmortem (performed at another hospital) the large left thoracic wall mass measured 15 by 10 by 4 cm It was composed of dilated vessels subcutaneous tissue and muscle The vessels appeared to be mainly tortuous elongated veins arising from the intercostal veins There was no obvious arteriovenous communication within the mass (postmortem injection study was not performed) The vascular mass extended from the subcutaneous area to the subpleural space The pleural space between the vascular mass and the left lung was obliterated by firm fibrous adhesions In it no vessel of significant caliber was observed

The lungs weighed 1 900 grams each The pulmonary artery showed no atheromatous plaques and no gross evidence of arteriovenous communications was observed in the lungs (injection studies were not done) The pleural spaces were free of adhesions with the exception of the area adjacent to the thoracic mass The heart weighed 480 grams and demonstrated no valvular lesion The thickness of the left ventricular wall at the apex was 1 0 cm that of the right ventricle was 0 2-0 3 cm The myocardium was flabby and of a reddish brown color The right ventricular endocardium was thicker than noted elsewhere The coronary arteries were patent

The liver weighed 1 150 grams Its surface was finely nodular the diameters of these nodules ranged from 2 to 5 mm Similarly the cut surface demonstrated the same nodularity altering the normal liver architecture Each pseudolobule was surrounded by a fairly uniform zone of fibrous tissue

Table III Pulmonary function studies in Case 13

	December 19 1	January 1954	Predicted value
Respiratory rate (per min)	16	20	—
Tidal volume (ml)	866	680	—
Resting ventilation (L /min)	13 9	13 6	—
Inspiratory capacity (L)	4 0	3 5	—
Vital capacity (L)	4 5 (112%)	4 49 (112)	4 0
Forced expiratory volume 3 sec (L)	3 75 (89%)	3 57 (84%)	4 3
Maximum breathing capacity (L)	110 (88%)	115 (92)	1 5
Functional respiratory volume (ml)	—	3 144	—
Expiratory reserve (ml)	—	1 350	—
Residual volume (ml)	—	1 94	1 37
Total lung capacity (ml)	—	6 714	5 533
$\frac{RV}{TC} \times 100$	—	26 7	<28
7 minute nitrogen elimination index of intrapulmonary gas distribution ( )	—	3 4	<2 5
Oxygen consumption (ml)	235	221	—
Oxygen removal rate (ml /L)	17	16 4	—
Arterial oxygen saturation (%)			
Room air Rest	75	69	>96
Exercise	65	62	—
100% oxygen Rest	100	100	100
Exercise	85	83	100

Represents the per cent of predicted normal value.

Table IV Per cent oxygen saturation of the blood samples withdrawn simultaneously from the brachial artery and the aneurysmal mass

Date	Brachial artery	Aneurysmal mass
May 1950	81	81
December 19 1	75	56
January 1954	69	73
February 1954	63	65

An increased number of bile ducts was noted The spleen weighed 300 gram It possessed thick capsule nd demonstrated the features of chronic passive congestion I the lower esoph gus many large thick walled eins were present in the sub mucosa and number of them extended to w thi several micra from the lumen of the esophagus Numerous dilated essels were present in the muscu laris layer and the surrounding tissue of the esophagus

Discussion

Arterial desaturation in patients with cirrhosis of the liver may result from either a decreased affinity of hemoglobin for oxy gen or from altered exchange of pul monary gases As to the former cause Rodman and co workers were unable to demonstrate any displacement of the oxyhemoglobin dissociation curve in their cirrhotic patients suggesting that the hemoglobin affinity for oxygen in a cir rhotic patient is normal With regard to the alternate cause cirrhotic patients have an increased tendency to develop frequent respiratory infections which may result in permanent changes in the lung tissue (fibrosis and thickened alveolar membrane) and a decrease in effective oxygen exchange Pulmonary venoarterial admixture occurs in the presence of perfused but hypo ventilated lung spaces It is reasonable to assume that ascites could have contributed to alterations in the relationships between ventilation and blood flow Such a state may be completely corrected by the breath ing of pure oxygen which results in vir tually complete equilibrium between the alveolar and arterial oxygen tensions[11] unless the venous admixture is due to a direct venoarterial communication in the lungs

A large A a gradient was demonstrated in 12 of these 15 patients after they had breathed pure oxygen for at least 30 min utes (Table II) These gradients corre sponded to venoarterial shunts ranging from 10 to 29 per cent of the respective cardiac outputs The pulmonary veno arterial shunting for the whole group averaged 18 per cent Although th degree of pulmonary shunting found in the patients of this study is similar to that found by Rodman and co workers[12] it is greater than that reported previously by others[14 15] This discrepancy in the re ported magnitude of the pulmonary ad mixture may be due to the severity and the duration of the liver disease and in part to the methods used in the respective studies In the 3 patients (Cases 3 7 10) who had normal A a gradients when breathing 100 per cent oxygen the observed hypoxemia when they were breathing room air must have been caused by one or more of the other factors discussed

Table V Findings at cardiac catheterization—Case 13

	Pressures (S/D) (mm Hg)	Oxygen content (vol %)	Oxygen saturation (%)	Dye curve AT (sec)	Dye curve PT (sec)
Pulmonary artery	24/11	11 98	64	6	11
Aneurysmal mass	44/33	14 59	73	14	16
Brachial artery	125/66	13 83	69		

Cardiac output 9 2 L /min
Cardiac index 4 9 L /min /M

T 1824 dye curve recorded by the ear-oximeter AT Appearance time PT Peak time



Fig 1 Photograph of the vascular mass in the left thoracic wall

above Ca es 3 and 10 had large ascites and Case 7 had a moderate collection of abdominal fluid

Two possible sites of venoarterial ad mixture in human beings with cirrhosis of the liver have been anatomically de scribed Calabresi and Abelmann [4] demon strated by colored plastic solution injected into the portal veins direct venous com munications between the periesophageal veins and the pulmonary veins at post mortem in only 2 of their patients with cirrhosis of the liver They postulated that venous admixture occurred through these channels The actual magnitude of such shunts would necessarily be greater than those which we est mated since the portal venous blood has a higher oxygen content than the mixed venous blood of the pul monary artery Portal hypertension was presumed to be responsible for the develop ment of shunting of venous blood from the portal to the pulmonary eins In Case 15 an estimated 21 per cent shunt was observed even after th portal vein was surgically anastomosed to the inf rior vena cava with alleviation of the portal h per tension thus suggesting th t the shunting measured is not directly related to portal hypertension

A second possibl site of venoarterial admixture is direct noncapillary communi cations of small pulmonary arteries with pulmonary veins as described by Rydell and Hoffbauer[1] and by Hales[10] and by Murray and co workers in juvenile and postnecrotic cirrhosis Normally in human beings as well as in animals arteriovenous anastomoses larger than capillaries exist in the lungs[11] Such anastomoses are known to be located beneath the visceral pleura and in the peribronchial area They can become functional under the impact of various stimuli [4]

These channels could conceivably open in the presence of a circulating vasodilator Such a substance might well originate in the cirrhotic liver or in the intestinal tract (as a metabolite) and can be shunted through the liver activating the pulmonary arteriovenous anastomosis The chemical nature of this vasodilator material has not yet been described A vasodepressor material (VDM or reduced ferritin) has been described by Shorr and co workers to be formed in the liver in the presence of hypoxia it is conceivable that the cirrhotic liver produces this material be cause of its reduced blood flow [7] The flavonoid rutin a specific antagonist of reduced ferritin reverted the peripheral circulatory changes in patients with clubbed digits to normal suggesting at least that in the cirrhotic patients with clubbing VDM may be present in the systemic circulation

The association of vascular mass (hemangioma or cirsoid aneurysm) and cirrhosis of the liver was briefly reported previously in 2 pat ents with se ere liver disease n one the vascular mass was located near the top of a buttock The vascular mass in our patient occurred spontaneously without known previous trauma It was considered to represent a collection of arteriovenous channels of the intercostal essels since its luminal pres sure was intermediate between that of the brachial and the pulmonary arteries (Table V) This mass emptied mainly into venous channel below the d aphragm as was demonstrated radiographically by the flow of the radiopaque material injected into its lumen—and also by the delayed systemic appearance of Evans blue d



Fig. 2. X-ray film of the radiopaque material injected into the thoracic vascular mass demonstrating its size and the flow of this material to neighboring vessels.

injected into its lumen as compared to an early appearance of the dye when it was injected into the pulmonary artery (Table V).

The oxygen saturation of the blood from the aneurysmal mass was essentially the same as that of a simultaneously drawn sample of arterial blood (Table IV). The comparatively high oxygen content of the sample of blood from the mass in 1954 along with pressure measurements suggested the presence of arterial connections with observed differences representing phasic variations in arterial saturation between the two sites. On one occasion the oxygen saturation of the blood obtained from the mass was lower than that found in the arterial blood, suggesting that fortuitously systemic venous blood was obtained. No pressure recording was made on that occasion.

Historically, the appearance of a small painless nontender mass in the left thoracic wall and its subsequent development to a larger mass suggested to us the presence of a circulating vasodilator material capable of enlarging nonpatent arteriovenous communications. In patients with cirrhosis, clubbing of the fingers and palmar erythema are associated with small arteriovenous oxygen and carbon-dioxide differences across the hands, suggestive of peripheral shunting presumably through the existing arteriovenous anastomoses in the hands.[9] It is postulated that this peripheral shunting was the result of an active circulating vasodilator.

Clinically, the findings of clubbing of the digits, cyanosis, secondary polycythemia, normal pulmonary function, and actively pulsating pulmonary arteries suggested the presence of pulmonary arteriovenous fistulae. The marked drop in the oxygen saturation of the arterial blood to 83 per cent and 85 per cent on two separate occasions (Table III) on moderate exercise during the breathing of 100 per cent oxygen is also characteristic of central venoarterial admixture. The portion of the cardiac output that was shunted at rest amounted to 24 to 25 per cent. Dye injection studies during right heart catheterization excluded intracardiac shunts; this was confirmed on postmortem examination. Therefore, it seems most likely that this is an example of intrapulmonary shunting. Unfortunately

no attempt was made at postmortem examination to demonstrate anatomically the existence of arteriovenous anastomoses or to localize the site of shunting by injection studies.

It is possible that two sites of pulmonary venoarterial shunting may be operating simultaneously or one may predominate in cirrhosis of the liver. The persistence of hypoxia and a large venoarterial shunt after portacaval anastomosis and the increased shunting in the reported case after exercise favor the hypothesis that venoarterial admixture is caused by direct communications of small pulmonary arteries and veins. Using isotope-labeled krypton (Kr^{85}), Fritts and co-workers[15] similarly observed that shunting occurred at both sites and found that the major fraction of the venoarterial admixture occurred between the portal and the pulmonary veins. But they pointed out that oxygen and krypton gas behave differently and suggested that these two methods probably detect different anatomic pathways. Further investigation is needed to elucidate the location and nature of these shunts.

Conclusions

A moderate degree of systemic arterial desaturation and an elevated alveolar-arterial oxygen tension gradient were found in 12 of 15 patients with cirrhosis of the liver. This was considered to be the result of venoarterial admixture. The magnitude of the shunt averaged 18 per cent of the cardiac output. Direct communications between the small pulmonary arteries and veins represent most likely a major cause of shunting.

An adult patient with alcoholic cirrhosis of the liver and a cirsoid aneurysm of the thoracic wall was described. The sudden appearance of the thoracic aneurysmal mass in the absence of trauma and its subsequent development suggests the possibility that such lesions may be due to the presence of a circulating vasodilator substance.

The clinical and laboratory findings of clubbed finger, polycythemia, arterial desaturation, and postexercise increase in the degree of pulmonary venoarterial admixture suggested the presence of pulmonary arteriovenous fistulae.

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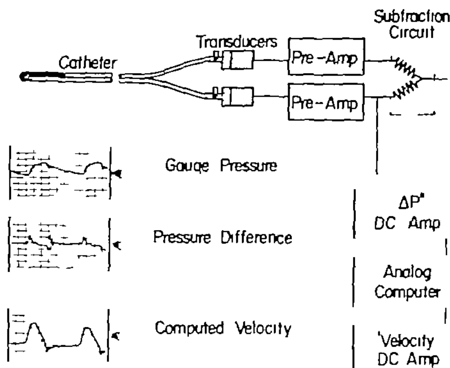


Fig. 1. A diagrammatic representation of the system used to assess instantaneous blood velocity in man. The method of application of the component parts are discussed in the text.

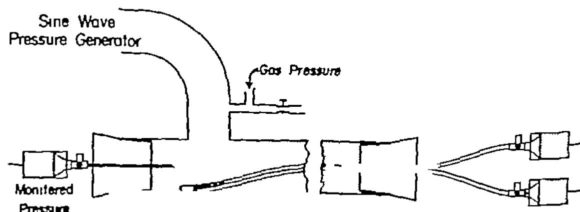


Fig. 2. The system used to evaluate the static and dynamic response of the catheter-gauge system under sterile conditions.

Gauges. The gauges used are Statham P 23Db gauges. We have used two other types of differential pressure gauges but have not found their performance characteristics as satisfactory as the two gauge Statham system. In order to obtain a differential pressure from two gauges it is useful to reverse the polarity of one of the gauges and then electrically sum the two signals. This is easily performed by reversing the leads of either the excitation circuit or the signal circuit on the gauge which is connected to the downstream orifices.

Amplifiers and electrical circuits. Each gauge is connected to a carrier preamplifier. We have used the Series 450 Sanborn preamplifier although any amplifier would

suffice that has extreme accuracy of setting and minimal base line and gain drift. As illustrated in Fig. 1, the single-ended outputs of each amplifier are connected to a subtraction circuit. The voltage output of this subtraction circuit is then amplified by a DC amplifier (the "Δ P" DC amplifier in Fig. 1) having fine control of the zero position and having minimal drift, since any base line shift will be magnified by the subsequent computation.

The instantaneous aortic blood velocity is continuously computed from the instantaneous pressure difference by an analog device which is either a passive network or preferably one including an operational amplifier.[3] In order to record the computed velocity adequately, further amplification may be necessary (the "Velocity" DC amplifier in Fig. 1).

The single-ended gauge pressure, the pressure difference, and the computed velocity can be recorded as illustrated in Fig. 1. A direct writing recorder has advantages since it is desirable to monitor immediately the pressure difference and computed velocity.

The problems encountered in setting up the amplifiers are threefold: (1) adjustment of the gains of the carrier preamplifiers so that the output voltage will always be in the linear range, (2) setting of the gains of the carrier preamplifiers to exactly equal each other, (3) fixation of the zero position so that when zero pressure is applied to both lumens the voltage output of the subtraction circuit is zero.

Calibration. The method of calibrating the system involves the application of a known constant pressure difference to permit a measure of the initial slope of the computed velocity versus time curve. The simplest way to apply a steady signal difference is to use the calibration button of one of the pressure amplifiers to obtain a constant voltage which can be calibrated as an equivalent constant pressure. The calibration factor, k, in units of centimeters

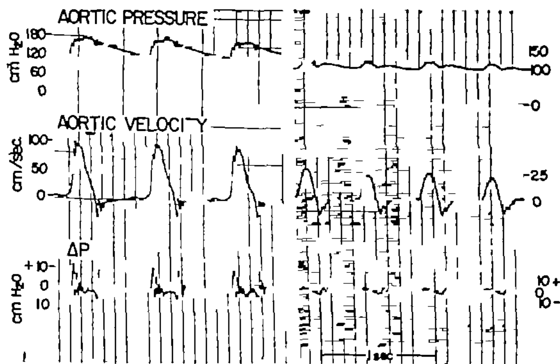


Fig. 3. On the left, from the top down, are the central aortic pressure, computed aortic blood velocity, and measured spatial pressure difference of a presumably normal 46-year-old man (C. H. 07 83-44). On the right are the same data for a 32-year-old man (R. F. 02 80 97) with severe myocardial insufficiency and mechanical pulsus alternans. Note that the calibration scales on the two records are different for the computed velocity and pressure difference.

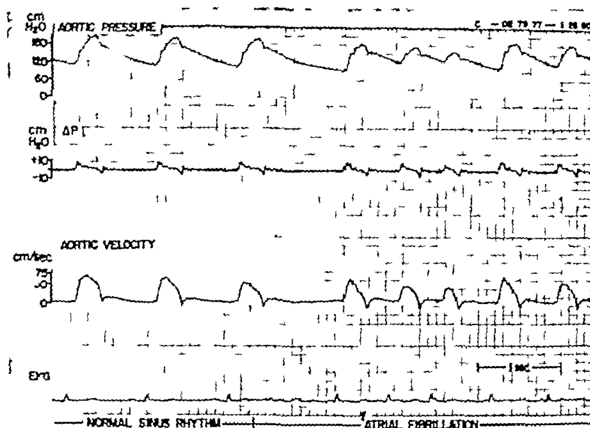


Fig. 4. A record of central aortic pressure, measured pressure difference, computed velocity, and electrocardiogram of a 46-year-old man with known myocardial fibrosis during spontaneous change from normal sinus rhythm to atrial fibrillation.

per second of velocity per millimeter of deflection on the record is then obtained from the following

$$k = \frac{P}{\rho} \cdot \frac{g}{\Delta x} \cdot \frac{1}{S}$$

where P is the equivalent pressure of the calibration signal in centimeters of H_2O (Gm./cm.²), ρ is the density of blood (1.05 Gm./cm.³), Δx is the catheter pressure tap separation (centimeters), g is the gravitational constant (980 cm./sec.²), and S is the initial slope of the computed velocity on the record (millimeters of deflection on the record per second).

Evaluation of catheter-gauge response. The main problem encountered with this system is the removal of all gas bubbles from the catheter-stopcock-gauge system so that optimal performance characteristics can be achieved. A good method for removing minute bubbles is to let a slow drip of sterile saline containing about 0.5 per cent of alcohol flow through each lumen for several hours.

The application of the computed pressure gradient technique to man requires that strict sterile procedure be maintained throughout. After sterilization of the catheter-gauge system* and immediately prior to the procedure, a careful evaluation of the static and dynamic performance characteristics of the system is carried out. The use of a long glass cylinder with a side arm as illustrated in Fig. 2 has been found to be convenient. The sterile catheter is placed in the previously sterilized tube. A sterile split rubber plug is used to close the opening around the catheter, and the tube is filled with 0.2 per cent benzalkonium chloride. Steady pressure can be applied to the system from a constant flow, high pressure source of gas through a connecting tube having a bleeder side arm which permits

*Sterilization of the catheter in this laboratory is performed with ethylene oxide gas.

the pressure to be adjusted to the desired level

The static response is evaluated by the application of a steady pressure to both lumens of the catheter simultaneously and the adjusting of the gain control on one of the carrier amplifiers so that the pressure difference indicated between the gauges remains near zero throughout the range of study An error of less than 0 3 per cent over the physiologic range can usually be achieved An error greater than this may introduce appreciable distortion in the measured pressure difference After both amplifier gauge systems are adjusted to have the same gain this gain is then calibrated against a water manometer by the application of a known pressure to one gauge while the other is held at a constant reference pressure

The dynamic response of the system is evaluated by applying a sinusoidal pressure to the air column in the upright side arm of the tube as illustrated in Fig 2 This sinusoidal pressure is imposed upon the constant base line pressure and is produced by a modified model airplane engine piston which is driven by a variable speed motor The pressure in the fluid near the tip of the catheter is directly measured for comparative purposes by a separate gauge trocar system that is dynamically accurate through 40 c p s At the present time we believe that each side of the catheter should have less than a ± 3 per cent amplitude error and no appreciable phase dis

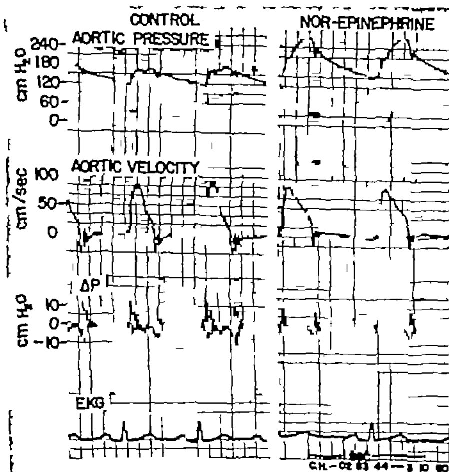


Fig 5 A record of the effect of intravenous norepinephrine upon the central aortic pressure computed blood velocity and measured pressure difference in a presumably normal 46-year-old man

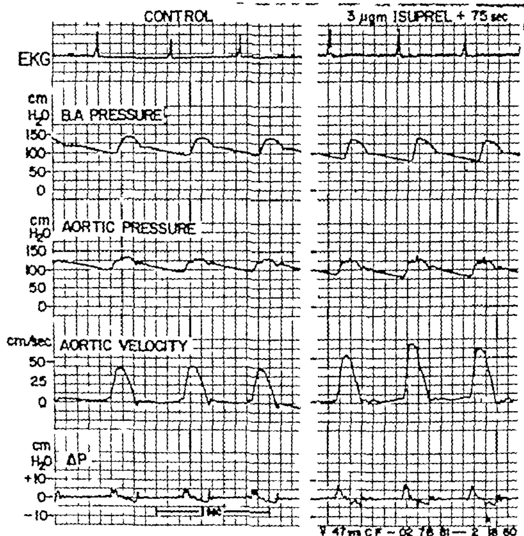


Fig. 4. A record of the effect of intravenous isoproterenol (Isuprel) upon the electrocardiogram, brachial arterial and central aortic pressure, computed aortic blood velocity, and measured pressure difference in a 4[illegible]-year-old woman with known endocardial fibrosis.

tortion through frequencies up to 12 c.p.s. to obtain a useful pressure difference. In addition, we have arbitrarily required that the maximum difference between the response of each side of the system be less than 5 per cent of the driving pressure when the same sinusoidal pressure (through frequencies up to 12 c.p.s.) is applied to both lumens of the catheter. There may be significant information in the pressure difference contained in frequency components above 12 c.p.s., but with the present technique such information will be distorted.

By means of sterile techniques the catheter is removed from the glass tube and the entire system is placed on the catheterization table. After adequate local anesthesia the femoral artery is entered percutaneously by a modified Robb needle. The catheter is advanced into the aorta and the needle is pulled back over its proximal portion. Pressure to prevent bleeding from the site of puncture is usually required during the entire procedure. Every 3 to 5 minutes the catheter is flushed with a heparin saline solution. Under fluoroscopic control the catheter is advanced until the tip is in the ascending aorta approximately 3 to 5 cm. above the aortic valves. It is frequently necessary to advance or withdraw the catheter

slightly to place the pressure taps down stream from the aortic valves and upstream from the innominate artery so that the necessary hydrodynamic assumptions are met[1] For the present the chief criterion for correct position is that the computed velocity corresponds to zero during the latter part of diastole

Application in the intact human being In this section data from a number of studies are presented The finer details of the velocity contour must be interpreted with caution since the coefficient of blood friction used in the velocity computation had to be chosen arbitrarily as previously presented[1] The contour of the velocity curve in the ascending aorta of a presumably normal 46 year old man is illustrated on the left side of Fig 3 The velocity tracing obtained from a 32 year old man with active myocarditis and congestive heart failure is shown on the right side of Fig 3 This latter curve represents one of the more marked deviations from normal that we have observed A mild mechanical alternans is more noticeable in the velocity tracing than in the aortic pressure curve In a 46 year-old patient with known myocardial fibrosis the rhythm spontaneously changed from normal sinus rhythm to atrial fibrillation as shown in Fig 4 A decrease in ejection velocity is noted when the diastolic filling time is shortened and/or atrial loading of the ventricle is lost

Ejection velocity was also measured after the administration of various drugs which are known to alter the myocardial contractility and peripheral resistance Norepinephrine is known to increase myocardial contractility[4] as well as to increase peripheral resistance resulting in an increase in stroke volume with a minute output that may be unchanged or decreased[4] As illustrated in Fig 5 norepinephrine given intravenously in an amount necessary to raise the systolic blood pressure 90 cm H O caused an increase in the duration of effective blood ejection as well as a

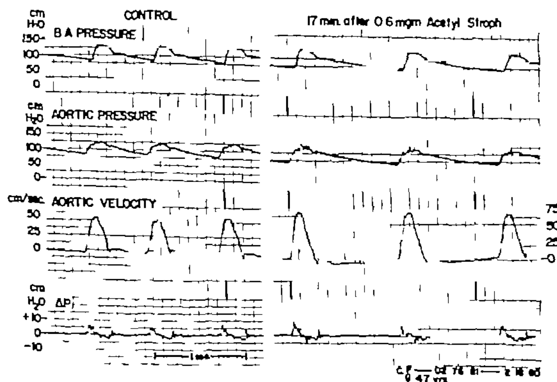


Fig 7 A record of the brachial arterial and central aortic blood pressure computed aortic velocity and measured pressure difference obtained just prior to and 1 minutes after the intravenous administration of 0 6 mg of acetyl strophanthidin to 47 year-old woman with known endocardial fibrosis

minimal decrease in peak ejection velocity. Isoproterenol has been shown[3] to cause an increase in heart rate and stroke volume. This is illustrated in Fig. 6; the administration of isoproterenol resulted in a marked increase in acceleration and peak ejection velocity, with a decrease in ejection time.

The administration of acetyl strophanthidin—a rapid-acting digitalis preparation—to patients with congestive heart failure is known to cause a rapid increase in stroke volume and a slowing of the pulse.[6] It was observed that this agent usually caused a definite increase in ejection velocity. The increase in velocity was found in those patients with clinically evident myocardial insufficiency, and also occasionally in patients with no objective evidence of cardiac disease. Fig. 7 illustrates the change which occurred 17 minutes after the intravenous administration of 0.6 mg. of acetyl strophanthidin to a 47-year-old woman with known endocardial fibrosis.

Summary and conclusions

Under restrictions outlined elsewhere[1] the instantaneous aortic blood velocity may be estimated by computation from the spatial pressure gradient. The methods used in this laboratory to apply this technique to the intact human subject have been presented. The final evaluation of the clinical usefulness of this technique will require its application to a much larger number of normal and diseased subjects. However, these preliminary studies indicate that nonvalvular myocardial disease is accompanied by changes in the pumping mechanism which result in alterations in the ascending aortic blood velocity contour. The changes in ejection velocity which occurred after the intravenous administration of norepinephrine, isoproterenol, and acetyl strophanthidin are consistent with previously known information about these drugs.

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Addendum

Since acceptance of this manuscript for publication, Porjé and Rudewald in Sweden have published their studies[7] on the computation of aortic blood velocity in man by means of a differential pressure technique. In the derivation of their computation, the flow is assumed to be nonviscous, in contrast to the derivation[1] used in this study, wherein the viscous as well as the inertial forces are considered.

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Relationships between left ventricular ejection time, stroke volume, and heart rate in normal individuals and patients with cardiovascular disease

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Although considerable attention has been focused in recent years on the alterations in central pressure and blood flow in various cardiovascular diseases, there has been relatively little study of the temporal phenomena in cardiac contraction in these states. In 1904 Bowen[1] employed the carotid pulse tracing to assess the duration of left ventricular ejection in man. In 1926 Lombard and Cope, applying this technique, observed an inverse relationship between heart rate and ejection time in normal human subjects. Later studies in animals demonstrated, in addition, a direct relationship between the cardiac stroke volume and ejection time.[2-4] In experimental studies of the ejection dynamics in various cardiovascular disorders only the effects of acutely induced lesions have been studied. Previous applications of these techniques to the study of ventricular ejection in patients with cardiovascular disease have not employed the indicator dilution or the Fick principle in estimating the magnitude of the blood flow. The ready availability of these techniques in the present-day cardiovascular laboratory, together with the stimulus provided by previous experimental studies, has prompted the current reinvestigation of these relationships.

Methods and materials

Observations were made in 60 normal male subjects who ranged in age from 23 to 64 years, and in 61 male patients with various forms of heart disease.

The cardiac output was determined by either the indicator dilution method or the direct oxygen Fick technique. When the indicator dilution method was used, indocyanine green dye was injected through an intracardiac catheter into the superior vena cava or pulmonary artery. The concentration of indicator dye was continuously measured in peripheral arterial blood by withdrawal of blood through a cuvette densitometer by means of a constant rate motor-driven syringe. The amplified dye dilution curve was recorded on a multi-

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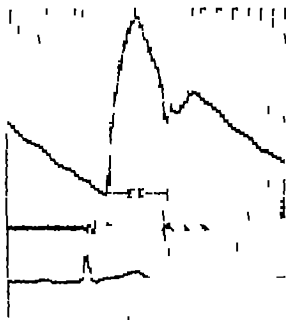


Fig 1 Simultaneous carotid pulse tracing, apical phonocardiogram and electrocardiogram illustrating the measurement of the ejection time from the upstroke to the incisura of the carotid pulse tracing Time markings indicate 0 02 second interval

channel photographic unit from which analysis of the time concentration curve was made When the Fick method was utilized arterial and mixed venous (pulmonary artery) oxygen content was determined by the method of Hickam and Frayser[8] The expired air was collected in Douglas bags over a 2 to 3 minute period and the gas analyses were made by means of the Pauling oxygen analyzer Simultaneous determinations of cardiac output by the two methods were made in 19 of the patients in the present series The range of cardiac output was 2 81 to ?7 L per minute With use of the Fick method as a standard the indicator-dilution determinations varied an average of 4 6 per cent (S D ± 3 7 per cent) with a maximum variation of 1?7 per cent No systematic difference between the two methods was observed Since congestive heart failure was present in a large number of the patients studied making estimations of nonedematous weight difficult the cardiac outputs rather than the cardiac indices are reported Stroke volume (S.V) was derived from the cardiac output and heart rate

The left ventricular ejection time (L T) was determined from external pulse tracings which were obtained by placing a standard funnel shaped pickup externally over the point of maximum pulsation of either the carotid or subclavian artery The signals were amplified through a strain gauge or piezoelectric apparatus and recorded on a multichannel photographic unit A standard electrocardiogram and an apical phonocardiogram were recorded simultaneously All recordings were made at a paper speed of 100 mm per second with the time markers indicating 0 02 second intervals The ejection time was measured from the beginning of the upstroke to the trough of the incisural notch (Fig 1) Care was taken to obtain tracings which clearly delineated these points By this technique the duration of ejection could be determined accurately to the nearest 0 01 second In each individual 5 to 10 consecutive complexes were measured and the average was recorded to the nearest 0 005 second Beat to beat variation did not exceed 0 01 second over the respiratory cycle when the R R interval remained constant When auricular fibrillation was present the R R interval corresponding to the average heart rate during the determination of cardiac output was selected and the succeeding complex measured The average of 5 to 10 such beats was recorded as the ejection time The mean rate of left ventricular ejection (MRLVE) was calculated from the ratio S V E T and is expressed in milliliters per second of ejection In all studies a steady state as evidenced from the monitored pulse rate and arterial pressure was achieved during the determination of the cardiac output and ejection time The pulse tracings were recorded immediately before and after the determination of the cardiac output

Table I Comparison of ejection time from carotid pulse tracing and central aortic pressure curve

Subject	Ejection time (sec) (central aorta)	Ejection time (sec) (external carotid pulse tracing)
F T	0 3 0	0 350
F K	0 320	0 310
W R	0 210	0 210
? H	0 265	0 265
? H	0 310	0 300

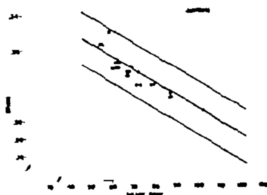


Fig 2 Relationship between ejection time and heart rate in normal individuals

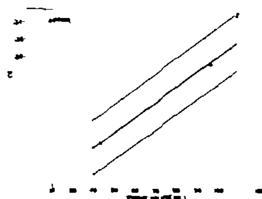


Fig 3 Relationship between ejection time and stroke volume in normal individuals

The ejection times derived from the simultaneous recordings of undamped central aortic pressure curves obtained by retrograde arterial catheterization and carotid or subclavian pulse tracings were compared in 5 individuals. A close agreement in the ejection times as determined by the two methods was observed (Table I), validating the measurement of ejection time from the pulse tracings as an index of left ventricular ejection time. The recording of brachial arterial pressure did not offer a reliable method for determining the ejection time because of the generally poor delineation of either the upstroke or the incisural notch in the tracings when fast paper speeds are employed.

All measurements of pressure were made by means of a Statham strain gauge transducer (P23D). The zero level for pressures was taken as 5 cm. below the angle of the sternum when the subject was in the supine position. Respirations were recorded by means of a standard pneumograph.

Statistical analyses of the data were performed according to the methods of Snedecor.[9]

Results

Normal individuals. Observations on the duration of left ventricular ejection and heart rate were made in 60 normal resting supine male subjects; these included 52 hospitalized patients without cardiovascular disease and 8 normal university students. The relationship between the duration of ejection and heart rate is demonstrated in Fig. 2. As heart rate increased over the range of 49 to 120 beats per minute, the ejection time diminished linearly. The value for the correlation coefficient of $-.90$ was significant ($p < .01$).

Seventeen of the 60 normal subjects were selected for more detailed analysis of the relationships between ejection time, heart rate, stroke volume, and the mean rate of left ventricular ejection. In order to obtain observations at the lower levels of stroke volume, we studied 5 of these subjects in both the supine position and in the 45-degree head-up tilt position. The data are summarized in Table II.

As stroke volume increased from 43 to 109 ml., ejection time increased linearly (Fig. 3). The value for the correlation coefficient was $+.93$ ($p < .01$). The ejection time was likewise well correlated with the stroke index ($r = +.88$, $p < .01$). The

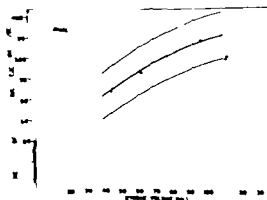


Fig. 4 Relationship between stroke volume and the mean rate of left ventricular ejection in normal individuals

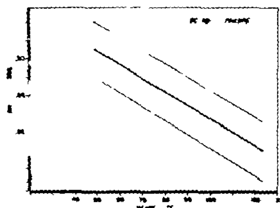


Fig 5 Relationship between ejection time and heart rate in myocardial failure The regression lines shown are those for the normal group

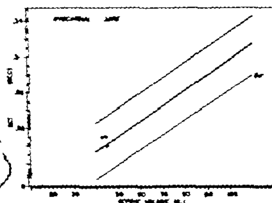


Fig 6 Relationship between ejection time and stroke volume in myocardial failure The regression lines shown are those for the normal group

regression equations appear in Table III

In Fig 4 the relationship between stroke volume and the mean rate of left ventricular ejection (MRLVE) is shown The MRLVE was derived from the relationship S V /E T Over the normal range of stroke volume the mean rate of left ventricular ejection varied from 220 to 382 ml per second of systole and increased in a curvilinear fashion with stroke volume

The relative contributions of the stroke volume and heart rate in the determination of the ejection time were further analyzed by multiple regression The regression equation appears in Table III It is apparent from this analysis that both stroke volume and heart rate contribute significantly to the ejection time in normal individuals

Myocardial failure The effect of myocardial failure and cardiac enlargement on the temporal dynamics of left ventricular ejection were studied in 12 patients with nonvalvular heart disease (Table IV) Etiologically the patients fell into three groups 4 with arteriosclerotic cardiovascular disease 6 young adults with idiopathic cardiomegaly and heart failure and 2 individuals with hypertensive arteriosclerotic heart disease but with normal levels of arterial diastolic pressure at the time of study All of the patients were males and demonstrated clear radiologic evidence of cardiomegaly Six were classified clinically as having severe heart failure and the other 6 had mild to moderate heart failure at the time of the study All of the patients had normal sinus rhythm and normal QRS conduction on the electrocardiogram Half of the patients were digitalized whereas half had received no digitalis therapy prior to the study The hemodynamic data are summarized in Table IV

In Fig 5 the relationship of heart rate and ejection time in the patients with myocardial failure is compared to the normal regression data The cardiac output in this group ranged from 2 1 to 5 8 L per minute with a mean of 3 6 L per minute The heart rate ranged from 53 to 108 per minute with an average of 76 (S D ± 16) representing no significant difference in heart rate from that of the normal group Nine of the 12 patients demonstrated a significantly decreased ejection time relative to heart rate Each of these 9 individuals had a cardiac output of 4 0 L

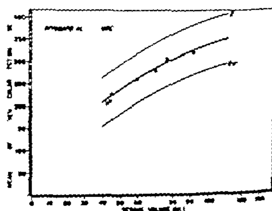


Fig 7 Relationship between stroke volume and mean rate of left ventricular ejection in myocardial failure The regression lines shown are those for the normal group

or less. The decrease in ejection time relative to heart rate in the patients with heart failure was significant ($p < .05$).

The relationship between stroke volume and ejection time in the patients with myocardial failure is summarized in Fig. 6. When compared to the normal regression data, no significant difference was observed; the values for 10 of the 12 patients fell within the expected normal range of ejection time for stroke volume. The stroke volume rather than the stroke index was employed in this and subsequent comparisons, since the inclusion of an indeterminate amount of edematous weight in the calculation of the body surface area in patients with congestive heart failure may yield erroneous estimates of the stroke index. In 2 patients rapid digitalization with deslanoside (Cedilanid) administered as a single dose of 1.6 mg. intravenously induced slight increases in stroke volume 1 hour later (8 and 4 ml., respectively) while heart rate remained unchanged. At this time the relationship between stroke volume and ejection time remained within normal limits.

The relationship between the mean rate of left ventricular ejection and stroke volume for the 12 patients with myocardial failure is shown in Fig. 7. When compared to the normal regression data, no significant difference was apparent; the values for 11 of the 12 patients fell within 2 standard deviations of the normal regression line.

Aortic valvular disease. The relationship between ejection time and stroke volume was studied in 16 patients with aortic

Table II. Hemodynamic data in normal subjects

Subject	Position	Cardiac output (L./min.)	Heart rate	Stroke volume (ml.)	Ejection time (sec.)	Mean rate of left ventricular ejection (ml./sec.)
A A	S	5 58	68	8	0 270	304
J P	S	5 51	68	81	0 275	295
L P	S	5 23	85	62	0 235	264
H W	S	6 78	72	9	0 265	358
V C	S	4 9	49	98	0 290	338
C W	S	5 33	120	44	0 200	220
F H	S	5 94	56	106	0 315	337
S I	S	6 09	60	103	0 320	319
J W	S	6 31	66	96	0 310	310
D W	S	5 36	65	82	0 285	288
H T	S	5 17	56	9	0 305	302
J G	S	5 29	72	4	0 260	285
E M	S	6 65	62	107	0 300	357
	T	4 53	93	49	0 200	245
W H	S	6 31	68	93	0 2 0	344
	T	5 94	84	71	0 235	302
J Y	S	5 3	57	101	0 305	331
	T	4 0	80	59	0 40	246
H R	S	7 06	65	109	0 285	38
	T	5 63	74	76	0 240	317
S W	S	6 33	80	9	0 250	316
	T	4 29	100	43	0 190	226

S, Supine; T, 45-degree head-up tilt.

Table III. Summary of regression data in 17 normal male individuals

E.T. = .266 – .0021 (H.R. – 73)	$p < .01$
E.T. = .266 + .0017 (S.V. – 8)	$p < .01$
E.T. = .266 + .0032 (S.I. – 43)	$p < .01$
E.T. = .266 + .0011 (S.V. – 8) – .0009 (H.R. – 73)	$p < .01$ (S.V.) $p < .05$ (H.R.)

E.T., Ejection time; H.R., Heart rate; S.V., Stroke volume; S.I., Stroke index.

Table IX Hemodynamic data in patients with cardiovascular c

Patient	Diagnosis	Cardiac output (L/min)	Heart rate	Stroke volume (ml)	Ejection time (sec)	Arterial blood pressure (mm Hg)
		Uvex I If dise				
D W	ASHD*	5	61	43	0 30	170 55
K B	ASHD	5 67	6	5	0 50	130 65
D J	ASHD*	4 19	1	45	0 200	170 4
J I	ASHD	2 81	6	3	0 255	1 55
S H	IMI	2 17	109	70	0 1 0	176 91
L S	IMI	5 15	90	59	0 0	14 98
O H	IMF*	3 47	71	35	0 55	105/69
V W	IMF*	3 0	65	57	0 40	155 55
R I	IMI*	4 01	37	0	0 50	107/64
F C	IMF*	3 41	92	1	0 190	170/ 5
L C	HASHD	3 2	5	43	0 10	1 4 55
J C	HASHD	4 56	53	9	0 95	165/71
		Mitral valvular disease				
L H	MS	4 5	9	57	0 50	1 7/84
H Q	MS-MI	3 95	90	44	0 33	106/ 0
M C	MS-MI	4 5	4	58	0 50	—
D W	MS-MI	4 66	64	73	0 0	123/ 4
G I	MS	6 0	60	100	0 305	95/50
W W	MS MI†	6 75	100	6	0 0	97/47
T N	MS-MI	5 0	61	59	0 83	1 8/55
H W	MS-MI†	5 45	90	61	0 55	101/58
K D	MS	3 93	5	50	0 235	1 4/ 4
V P	MS MI	4 00	56	71	0 370	105/ 0
S H	MS-MI	5 01	60	54	0 305	155/66
J C	MS-MI	3 35	57	64	0 300	136 63
		Other disease				
C M	RHD	6 11	63	9	0 3 5	—
L S	RHD	5 09	0	73	0 345	11 /65
J D	RHD	4	54	5	0 350	105/6
S B	CAS	3 4	59	55	0 50	140/68
M P	CAS	2 91	0	4	0 0	1 3/81

Patient	Diagnosis	Cardiac output (L/min)	Heart rate	Stroke volume (ml)	Ejection time (sec)	Arterial blood pressure (mm Hg)
			Hypertension			
J W	HCVD‡	4 93	55	43	0 30	11
D S	HCVD‡	97	5	40	0 305	1 4 101
D H	HCVD‡	69	6	43	0 195	1 1 11
D S	HCVD	6 59	69	96	0 260	50 1 1
H W	HCVD	6 2	9	65	0 205	250/136
W K	HCVD	5 05	2	0	0 7 0	211/1
H W	HCVD	5 41	50	1	0 5	19 /101
H F	HCVD	6 90	4	91	0 55	50/134
K W	HCVD	4 50	59	54	0 300	217/149
W S	HCVD	5 70	52	100	0 260	270 1 4
W J	HCVD	6 63	90	4	0 215	160/101
			Aortic insufficiency			
C F	SHD	5 05	60	54	0 350	160/51
W C	SHD	4 10	55	75	0 365	16 /35
C I	SHD	4 57	50	57	0 3 0	199 55
C H	SHD	3 55	6	57	0 290	135/43
H H	RHD	5 12	8	64	0 310	195/ 0
J S	RHD	6 44	55	117	0 335	13 /61
J S	RHD	6 4	85	73	0 3 5	15 /79
B J	RHD	6 05	65	91	0 370	121/59
F I	RHD	4 51	0	64	0 360	160/50
C L	RHD	5 94	54	110	0 315	134/ 0
W C	RHD	5 33	66	51	0 375	14 /90
J H	ASHD	3 79	102	3	0 200	134/76
Z J	ASHD	3 45	57	61	0 290	160/48
D W	ASHD	3 11	61	51	0 290	136/59
J V	HCVD	4 34	69	65	0 300	210/95
J C	HCVD	5 2	72	45	0 55	225/1 3

*Mild angina pectoris.
†Mild mitral insufficiency.
Hypertensive cardiovascular disease with myocardial failure.
ASHD, arteriosclerotic heart disease; IMF, ... myocardial fibrosis; HASHD, Hypertensive and arteriosclerotic heart disease; HCVD, Hypertensive cardiovascular disease; MS, mitral stenosis; MI, mitral insufficiency; RHD, rheumatic heart disease; CAS, ... HD ...

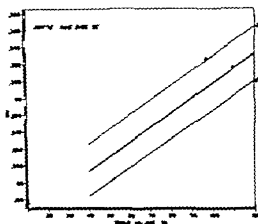


Fig 8 Relationship between ejection time and stroke volume in aortic valvular disease The normal regression lines are shown *AI* denotes patients with aortic insufficiency *AS* denotes patients with aortic stenosis

insufficiency and in 5 patients with isolated aortic stenosis Only patients who had pulse tracings which revealed accurate delineation of the upstroke and incisura were studied

The patients with aortic insufficiency represented rheumatic syphilitic arteriosclerotic and hypertensive etiologies Ten of the group demonstrated obvious peripheral signs of aortic insufficiency whereas in 6 a diastolic murmur was the sole clinical finding to indicate aortic regurgitation None of the patients demonstrated auscultatory evidence of mitral stenosis or mitral insufficiency The mean heart rate for the group was 68 (S D ±13) which represented no significant difference from the heart rate in the normal group

In the 5 patients with aortic stenosis objective evidence of stenosis was provided in 2 by retrograde arterial catheterization of the left heart and in 1 by later post mortem examination The other 2 patients demonstrated clear clinical signs of aortic stenosis without aortic regurgitation The data are summarized in Table IV and Fig 8

Thirteen of the 16 patients with aortic insufficiency demonstrated a prolongation of the ejection time relative to stroke volume when values for them were compared to the normal data (Fig 8) The 3 patients in whom the values fell within normal limits were among the individuals who demonstrated only the basal diastolic murmur of aortic regurgitation without peripheral signs Each of the patients with aortic stenosis demonstrated prolongation of the ejection time relative to stroke volume

The relationship of the pulse pressure to the degree of prolongation of the ejection time (observed value *minus* expected normal regression value for the stroke volume) for the 16 patients with aortic insufficiency is illustrated in Fig 9 A significant correlation between the degree of prolongation of ejection time and the pulse pressure in aortic insufficiency was observed ($r = +.57$ $p < .01$)

In order to test further whether prolongation of ejection occurs in isolated aortic stenosis we surveyed the literature to collect the cases of aortic stenosis for which stroke volume and systolic ejection periods derived from the aortic pressure pulse were published The complete studies of Goldberg Smith and Raber[3] on patients with isolated aortic stenosis offered an opportunity to compare our data in normal subjects with the data in 26 such patients who had calculated aortic valvular areas which ranged from 0 2 to 1 2 cm (Eleven of the patients in the Goldberg series in whom ejection time was estimated from the brachial arterial pulse were not included for comparison) Twenty two of the 26 patients with aortic stenosis demonstrated a prolongation of ejection time relative to stroke volume when their values were compared to the data for the normal group (Fig 10) All of the patients with a cal

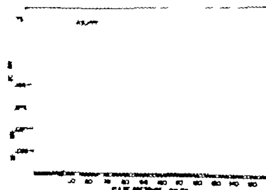


Fig 9 Relationship between the degree of prolongation of ejection time and pulse pressure in aortic insufficiency

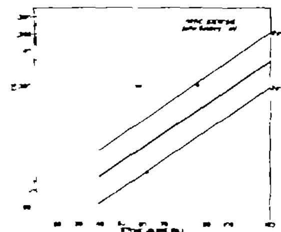


Fig 10 Relationship between ejection time and stroke olume in 26 patients w th isolated aortic tenosis (from the data of Goldberg Smith and Raber[19]) The regres ion lines are those for the normal group

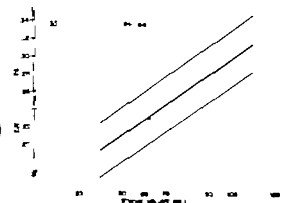


Fig 11 Relation hip between ejection time and stroke olume in mitral alvular disease The normal regres ion lines are hown

culated valvular area of 0 5 cm or less had a prolonged ejection time Of the 4 patients with a normal ejection time 2 had a calculated valvular area of 1 1 and 1 2 cm ^{2} representing the largest calculated valvular areas for the group

Mitral valvular disease The relationship between ejection time and stroke volume was studied in 9 patients with mitral valvular disease All of the patients were studied prior to surgical exploration and mitral valvulotomy Evaluation of the function and ize of the valve was per formed at the time of valvulotomy The area of the mitral valve was estimated to be 1 0 cm or less in 7 of the patients and 1 5 cm in 2 of the patients At the time of the operation the surgeon evaluated each valve for the presence of mitral re gurgitation Three of the patients demon strated no palpable mitral insufficiency at the time of operation whereas 4 had mild and 2 had moderate mitral regurgitation In 3 of the group a basal diastolic murmur thought to represent pulmonary insuffi ciency (Graham Steell) was heard

The data are summarized in Table IV and Fig 11 Four of the patients had *cardiac outputs of 4 5 L per minute or* less whereas the others had a cardiac output that was in the normal range Auricular fibrillation was present in 5 of the patients The mean heart rate for this group was 78 (S D ±15) which repre sented no significant variation from the normal data for cardiac rate

Values for 8 of the 9 patients fell within normal limits with respect to the relation ship of ejection time to stroke volume (Fig 11) Although a tendency for the data to be distributed in the upper normal range of ejection time was noted this represented no significant variation from the findings in the normal group

Three additional patients with combined mitral stenosis and aortic insufficiency as sociated with wide pulse pressures were studied Each of these individuals demon strated a prolongation of ejection time relative to stroke volume

Hypertension The ejection time was studied in a group of 11 patients with severe hypertension (Table IV Fig 12) The systolic arterial pressure ranged from

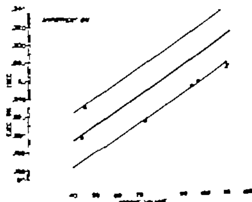


Fig 12 Relation hip between ejection time and troke olume in hyperten disease Patient with con estiv heart failure are designated by the open squares The normal regres ion lines are hown

160 to 256 mm. Hg, whereas the diastolic pressure ranged from 104 to 149 mm. Hg. Eight of the patients had no clinical evidence of congestive heart failure, whereas 3 had clinically apparent signs of congestive heart failure at the time of the study. The mean heart rate of 77 (S.D. ±13) for the group was not significantly different from that for the group of normal individuals.

Fig. 12 illustrates the relationship between stroke volume and ejection time for the group compared to the normal regression data. The 8 patients without congestive heart failure all had normal cardiac indexes. Although 7 of these 8 patients tended to have a low ejection time relative to stroke volume, this represented no statistically significant variation from the findings in the normal group. The 3 patients with cardiac failure and hypertension were not included in the previous series of patients with myocardial failure. Each of these 3 individuals had values which fell within normal limits of ejection time relative to stroke volume.

Pericardial disease and pulsus paradoxus. The respiratory effect on the ejection time in the presence of pericardial disease was studied in 2 patients with constrictive pericarditis and pericardial calcification (J.M., M.B.) and in 1 patient (W.P.) with pericardial effusion. The 2 patients with constrictive pericarditis demonstrated a variation in systolic arterial pressure of 28 and 34 mm. Hg, respectively, over the respiratory cycle at rest. The patient with pericardial effusion demonstrated a systolic variation of 6 mm. Hg during quiet breathing. In all 3 patients a significant change in ejection time, which ranged from 0.025 to 0.050 second, was noted through the respiratory cycle at a time when the R-R intervals remained constant (Table V). This change consisted of a serial shortening of the ejection time at the onset of inspiration, reaching a minimum just preceding the end of inspiration and coinciding with the lowest systolic arterial pressure. In normal individuals studied during quiet respiration the left ventricular ejection varied no greater than 0.01 second when the R-R interval remained constant.

Discussion

The technique of recording the pulse tracing employed in this study offers a convenient means for assessing the duration of left ventricular ejection. It is of importance to emphasize that the duration of systole measured in this manner refers solely to the ejection or isotonic phase of cardiac contraction and does not include the periods of isometric contraction and isometric relaxation. Furthermore, the duration of ejection derived from the pulse tracing exceeds by a small time increment the true duration of isotonic shortening of the heart because of the slight delay in closure of the aortic valve.[3] Although this error in the time interval of ejection is a definite one, the interval between the termination of cardiac contraction and the closing of the aortic valve would appear to be sufficiently small relative to the over-all duration of ejection so as to not alter the data significantly.

Previous studies on the relationship between ejection time, heart rate, and stroke volume in human subjects and in patients with cardiovascular disease have employed

Table V. Phasic respiratory variation in ejection time and blood pressure in patients with pericardial disease

Patient	End inspiration			End expiration		
	Arterial blood pressure (mm. Hg)	R-R interval (sec.)	Ejection time (sec.)	Arterial blood pressure (mm. Hg)	R-R interval (sec.)	Ejection time (sec.)
J.M.	102/ 7	0.73	0.210	130/64	0.74	0.245
M.B.	150/80	0.78	0.220	184/90	0.78	0.270
W.P.	94/ 0	0.63	0.205	100/72	0.62	0.230

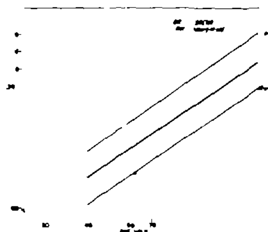


Fig *10* Relationship between ejection time and stroke olume in 26 patients w th isolated aortic steno is (from the data of Goldberg Smith and Raber[34]) The regression lines are those for the normal group

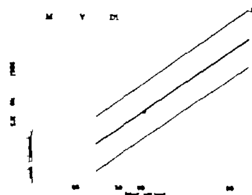


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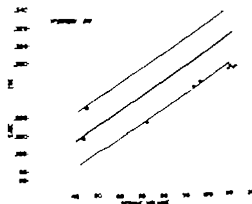


Fig *12* Relationship between ejection time and stroke olume in hyperten disease Patient with congestive heart failure are de ignated by the open squares The normal regression lines are shown

The prolongation of ejection time observed in experimentally induced[1] as well as clinically evident aortic insufficiency can be explained on a different basis. In aortic regurgitation the true cardiac stroke volume is greater than the peripheral or effective stroke volume. The duration of the aortic ejection is related to the true cardiac stroke volume as was demonstrated in the normal data. Therefore the prolongation of ejection time relative to the effective stroke volume can be attributed to the greater time spent in expelling the regurgitant volume. When the pulse pressure in the patients with aortic insufficiency was compared to the degree of prolongation of ejection a significant correlation was found. Such considerations suggest future studies on the use of these relationships as a means of estimating regurgitant flow in patients with aortic insufficiency.

When the relationship between heart rate and ejection time is considered in patients with hemodynamically significant aortic valvular disease prolongation of ejection time may not be observed in individuals with congestive heart failure. The decrease in ejection time relative to heart rate as a consequence of the low stroke volume in congestive heart failure may balance the prolongation induced by aortic valvular disease. Prolongation of ejection time relative to stroke volume in these patients is therefore a more predictable finding in the clinical analysis of these problems.

Previous studies in animals which attempted to assay the effects of hypertension have demonstrated a tendency for prolongation of ejection during sustained and severe increases in aortic pressure induced by mechanical outflow resistance. The present findings were of interest in that none of the individuals studied demonstrated prolongation of ejection time. Rather a normal and in some individuals a decrease in ejection time relative to stroke volume was observed. It is improbable therefore that the effects on left ventricular ejection of acutely induced aortic outflow resistance are comparable to the events in chronic hypertensive disease in human beings.

The observations on ejection time in patients with isolated mitral stenosis are consistent with the presence of normal left ventricular outflow dynamics in this disease. It is of note that gross prolongation of ejection as was observed in aortic insufficiency did not occur in the patients with mitral insufficiency. These observations suggest either that the regurgitant flow occurs at a very rapid rate relative to the aortic ejection or that the greatest volume of regurgitation occurs during the pre-ejection or postejection phases of ventricular systole. It is possible however that the magnitude of regurgitation in the patients studied was actually small relative to the peripheral stroke volume since individuals with free mitral regurgitation were not observed in the present series. It is of interest that in experimentally induced high grade mitral regurgitation left ventricular ejection was similarly unchanged.

The present technique affords a simplified approach to the study of beat to beat changes in stroke volume. In this regard the finding of a significant decrease in ejection time during inspiration in the patients with pericardial restriction when heart rate remained constant supports the thesis that a fall in stroke volume due to inspiration is the basis for paradoxical pulse.

Some further considerations relative to the temporal factors in cardiac contraction are worthy of notation. The relationships between heart rate stroke volume and ejection time are such that at a constant level of cardiac output the total duration of ejection per minute is greater at a high cardiac rate and low stroke volume than at a low heart rate and a high stroke volume. Excepting the minimum alteration in the duration of the isometric periods of contraction and relaxation which might occur with these changes in rate and stroke volume the duration of diastole per minute is shortest at fast heart rates and low stroke volumes. Although these alterations in diastolic time might be of little consequence in normal individuals they could play a significant role in patients with such conditions as mitral and tricuspid stenosis and coronary artery disease in whom the duration of diastole becomes a more important determinant of ventricular or coronary artery filling.

During the course of the present studies certain practical applications of the data have come to light. The recording of ejection time and heart rate alone may be of use in evaluating the level of cardiac output in patients with suspected heart failure, since a persistent decrease in ejection time relative to heart rate is indicative of a low stroke volume. In patients with a basal systolic or diastolic murmur, prolongation of ejection time relative to heart rate suggests hemodynamically significant aortic stenosis or aortic insufficiency. The technique may offer additional value in following up patients after operative procedures for these conditions. In view of the decrease in ejection time relative to heart rate occurring with congestive heart failure, the simultaneous determination of the cardiac output and stroke volume lends a greater specificity to the measurement of ejection time in the practical evaluation of patients with valvular heart disease.

Summary

In the present study the relationships between the ejection time, heart rate, and stroke volume in normal individuals and in patients with various cardiovascular disorders were investigated. Ejection time was measured from the carotid or subclavian pulse tracing, and stroke volume was derived from direct measurements of blood flow.

In normal individuals ejection time varied inversely with heart rate and directly with stroke volume. In patients with nonvalvular heart disease and cardiac failure, ejection time was usually low relative to heart rate but tended to fall within normal limits relative to stroke volume. At the level of stroke volume observed in the patients with congestive heart failure, the mean rate of left ventricular ejection was within normal limits.

Prolongation of ejection time relative to stroke volume was observed in patients with aortic insufficiency and in those with isolated aortic stenosis. The degree of prolongation in ejection time was well correlated with the severity of the aortic valvular disease.

In patients with mitral valvular disease, including isolated mitral stenosis as well as in those with mild to moderate mitral regurgitation, ejection time fell within the normal range relative to stroke volume.

In patients with severe hypertensive disease ejection time fell within the normal or low normal range relative to stroke volume. In 3 patients with pericardial disease an abnormal phasic respiratory variation in ejection time was observed.

The present observations on temporal phenomena in cardiac ejection suggests the practical application of these techniques in the evaluation of patients with various cardiovascular disorders.

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Effect of expiratory and inspiratory breath-holding on the lead field spatial vectorcardiogram

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After 50 years of electrocardiographic study there is still no unanimity of opinion concerning the fundamental cause of the changes in pattern observed during the respiratory cycle or at the extremes of expiratory and inspiratory breath holding.

The earliest qualitative observations were those of Samojloff,[1] Einthoven[2] and James and Williams,[3] but the first systematic studies were made by Einthoven, Fahr and de Waart,[4] Williams,[5] and Waller.[6] By 1920 Lewis[7] had declared that "it is certain that the electrical axis bears to the anatomical axis a certain relation . . . and that the former may be employed within certain limits in calculating the actual lie of the heart in the body." But to what extent anatomic displacement could be regarded as responsible for the respiratory changes in the electrocardiogram he was less sure and added that "there are other factors which come into play; for accompanying the acts of breathing the vagal tone alters and the shapes of the curves are thereby influenced; some change is also induced in all probability by rotation of the heart around its own axis."

Since then many authors (e.g., Cohn and Raisbeck, Herrmann and Wilson, Master,[10] Burch, Abildskov and Cronvich[11]) have confirmed the dependence of the electrocardiogram on cardiac anatomic position, but whereas most earlier workers had assumed that positional changes were chiefly responsible for the respiratory variations in pattern, subsequent investigators have tended to oppose that view and to implicate primarily nervous and hemodynamic factors. Woodruff,[1] on the basis of his own and Condorelli's[12] clinical observations, asserted that "the cause of the respiratory changes does not appear to be due to a shifting of the axis caused by movements of the diaphragm," and he invoked the influence of the vagus and sympathetic nerves, as well as variations in coronary blood flow, to account for the electrocardiographic findings.

In a recent study of the electrical changes during the respiratory cycle, Lamb[1] concluded that they could be correlated with expected differences in stroke volume of the right and left ventricles and were independent of varying cardiac position and autonomic nervous control. Similarly, Simonson, Nakagawa, and Schmitt,[15] investigating the electrocardiographic patterns resulting from the more static conditions of expiratory and inspiratory breath holding, were satisfied after statistical analysis that their data could not be explained adequately by anatomic factors alone.

In a detailed study during which he correlated functional residual volume with

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Table I. Effect of breath holding on mean heart rate and Q-T interval (Lead A)

	R-R	Heart rate	Q-T	Q-T / R-R	QT
Normal respiration	0.87 sec (S.D. 0.13)	69 per min (S.D. 10)	0.37 sec (S.D. 0.03)	0.43 (S.D. 0.05)	0.39 (S.D. 0.03)
Full expiration	0.86 (0.14)	70 (11)	0.36 (0.03)	0.43 (0.05)	0.39 (0.02)
	0.11, $t = 5.8$, $p < 0.01$	8, $t = 5.7$, $p < 0.1$		0.05, $t = (1$, $p < 0.01$	0.0?, $t = 6.1$, $p < 0.01$
Full inspiration	0.97 (0.16)	62 (11)	0.36 (0.03)	0.38 (0.05)	0.37 (0.0)

Table II. Effect of breath holding on RLF plane mean vector angles as determined from Limb Leads I and II

	Normal respiration		Full expiration		Full inspiration
QRS	66 (S.D. 23)		61 (S.D. 30)		75 (S.D. 13)
		5, $t = 2.6$, $0.02 > p > 0.01$		15, $t = 3.4$, $p < 0.01$	
T	42 (23)		35 (22)		50 (23)
		7, $t = 3.8$, $p < 0.01$		15, $t = 5.0$, $p < 0.01$	
QRS-T	+24 (29)		+26 (34)		+25 (28)
VG	54 (18)		47 (19)		64 (13)
		7, $t = 4.4$, $p < 0.01$		17, $t = 7.1$, $p < 0.01$	

cardiac electrical axis and radiologic appearance. Shephard[9] showed that normal quiet respiration produced a swing of 8 to 17 degrees in the frontal plane QRS vector (clockwise during inspiration) and that this degree of rotation on an anteroposterior axis was consistent with that observed radiologically. He also demonstrated that functional venesection by cuff occlusion produced minimal effects, suggesting that hemodynamics played only a minor part in determining the form of the electrocardiogram in his experiments.

Because of this conflict of opinion and the fact that almost all of the previous data have been obtained by means of the conventional RLF and chest leads which are now known to possess inherent fundamental disadvantages, it was considered of value to reinvestigate this problem by employing the theoretically more satisfactory orthogonal lead field system of

McFee and Johnston [7 8] and Jordan and Beswick at the same time that a survey was being carried out to determine the normal ranges of scalar and loop spatial observations in a group of male medical students Consequently a study was made of the loop and vectorial effects produced at the extremes of expiratory and inspiratory breath holding to be followed later by further investigations during the more dynamic circumstances of the active respiratory cycle

Method

Twenty nine of the 47 subjects for whom lead field scalar and loop spatial electrocardiographic data obtained during normal quiet respiration have been previously reported were studied further by the same technique at the extremes of breath holding

After a period of relaxation and quiet breathing while lying supine each subject was instructed to expire to the maximum short of physical straining and to hold the breath for about 10 seconds during which time Leads I and II were synchronously recorded at fast paper speed (100 mm per second) on a direct writing Liemit Elmqvist two-channel electrocardiograph This process was repeated twice for recording the lead field Leads A and B and B and C and a further twice for photographing the frontal and horizontal planar loops from the screen of a vectorscope Subsequently similar records were obtained during breath holding at maximal inspiration

The methods for calculation of vectorial quantities and the symbols and orientations adopted for the presentation of the vectors and loops were the same as those previously described

Results

Of the 29 subjects examined 23 were shown earlier to comprise a single homogeneous group when assessed on the basis of cardiac vectorial and spatial loop analyses whereas the other 6 showed individual peculiarities Consequently although we have included all 29 students in the time interval data of the present investigation the mean vectorial values have been presented for the group of 23 and those for the other 6 have been treated separately

Detailed analyses of the time intervals for all three orthogonal leads (A B and C) were made but only the results from Lead A are reported as being typical of all three leads and roughly comparable with the conventional RLF plane Lead I The theoretical limitations involved in deducing time intervals from a single lead instead of from the ideal arrangement of three synchronously recorded orthogonal leads have been stressed by Pipberger and Tanenbaum and Beswick and Jordan [22] but for comparative assessment of the cardiac responses induced by changes in physiologic environment it would appear that some valid information can be obtained from a single lead

The effects of respiratory changes on the mean heart rates for all the subjects are shown in Table I There was no significant difference between the rates during quiet breathing and those with the breath held in full expiration but when the breath was held in full inspiration a mean decrease of 8 beats per minute was observed

The duration of the Q T interval was the same in all three respiratory states but as a consequence of the increase in length of the cardiac cycle (R R) the ratio $\frac{Q\text{-}T}{R\text{-}R}$ was significantly decreased in full inspiration The corrected Q T interval (QT) of Bazett i e $\frac{Q\text{-}T}{\sqrt{R\ R}}$ which is commonly supposed to be constant irrespective of physiologic changes in heart rate was in this study also reduced in full inspiration

From Table II it appears that in the RLF plane as calculated from Lead I and II there are progressive shifts in vectorial position for both QRS and T and therefore for the ventricular gradient (VG) from full expiration through quiet respiration to full inspiration both vectors become more vertical by equal increments and thus leave the QRS T angle unaltered

Previously it has been shown that in both untrained students and international athletes[20] the majority of subjects breathing quietly give RLF plane vector angles which can be converted to the corresponding frontal plane values as given by the lead field technique by using a simple right angled isosceles triangular reference frame

Table III *Frontal plane mean vector angles derived from RLF plane data using a right angled isosceles triangular reference frame*[34]

	Normal respiration	*Full expiration*	*Full inspiration*
QRS	58 (S D 18)	56 (S D 22)	64 (S D 12)
		└── 8 ──┘ (expiration vs inspiration)	t = 3 1, p < 0 01
T	55 (15)	51 (14)	61 (16)
	└── 4 ──┘ (normal vs expiration) t = 3 3, p < 0 01	└── 10 ──┘ (expiration vs inspiration)	t = 5 2, p < 0 01
QRS-T	+ 3 (21)	+ 5 (24)	+ 3 (21)

instead of the Einthoven equilateral The data given in Tables III and IV demonstrate that this interconversion holds good in the conditions of extreme breath holding studied here since there are no statistical differences between the calculated and the observed vectorial angles

Since it can be seen from Tables IV and V that the lead field cardiac vectorial values were the same in both spatial direction and magnitude during quiet respiration and at full expiration all further statistical comparisons have been made only between the two extreme states of breath holding

There was no significant difference between the mean spatial QRS-T angles calculated for inspiration and those for expiration (Table IV) although the T vector became more vertical and anteriorly directed in inspiration At the same time the QRS vector moved only downward and through a smaller angle than T Therefore the QRS-T angle in the frontal plane was reduced and in the horizontal plane increased in inspiration with VG moving in the same sense as T

The mean spatial magnitudes for T and total QRS were both reduced in inspiration (Table V) by about 10 and 8 per cent respectively leaving their ratios unaffected

Fig 1 shows typical planar vectorcardiographic loops which illustrate the effects of the contrasting respiratory states and it is apparent that, in general inspiration produced more vertical QRS loops coupled with some anticlockwise rotation on a longitudinal axis and anterior displacement of the T loops In addition for the majority of subjects smaller voltages were recorded from the body surface during inspiration

The vectorial data for the 6 subjects of the subsidiary group are given in Table VI and representative planar loops are illustrated in Fig 2 These findings are considered separately at the end of the following discussion and compared with those of the main group

Discussion

Main group of 23 subjects The well known increase in heart rate associated with the act of inspiration is not maintained if the breath is held at the height of inspiration The reduced mean rate of 8 beats per minute observed in the present study confirms the conclusion of Lamb[1] and Lamb Dermksian and Sarnoff[2,3] that this is the most common response to breath holding at maximum voluntary lung inflation but the greatest individual reduction noted was only 20 beats per minute in contrast to the 50 quoted by those authors It should be emphasized that a reduction in rate was not an invariable finding since approximately 10 per cent of our subjects showed a small increase

Table IV Effect of breath holding on the lead field frontal and horizontal planar and spatial mean vector angles

	Normal respiration	Full expiration	Full inspiration	
		Frontal Plane		
$F\hat{A}_{QRS}$	60° (S D 17)	6 (S D 17)	66 (S D 14)	4; $t = 2\ 2$, $p < 0\ 05$
$F\hat{A}_{T}$	33 (15)	55 (15)	64 (15)	9; $t = 3\ 7$, $p < 0\ 01$
$F\hat{A}_{QRS\text{-}T}$	+ 5 (21)	+ 7° (21)	+ 2 (20)	5; $t = 2\ 6$, $p < 0\ 01$
$F\hat{A}_{G}$	59 (11)	59 (12)	6 (11)	8; $t = 6\ 0$, $p < 0\ 01$
		Horizontal Plane		
$H\hat{A}_{QRS}$	295 (20)	796 (20)	295 (20)	
HA	71 (11)	71 (12)	7 (10)	6; $t = 6\ 0$, $p < 0\ 01$
$H\hat{A}_{QRS}$	+133 (24)	+135 (24)	+142 (4)	7; $t = 4\ 3$, $p < 0\ 01$
$H\hat{A}_{G}$	52 (17)	54 (19)	60° (18)	6; $t = 5\ 5$, $p < 0\ 01$
		Spatial		
$(SP)\hat{A}_{QRS}$	+10? (17)	+104 (17)	+105 (21)	

Table I. Effect of breath holding on the lead field mean spatial vector magnitudes (in micro-volt-seconds)

	Normal respiration	Full expiration	Full inspiration
(SP)$\bar{A}_Q$	34 (S.D. 13)	31 (S.D. 13)	33 (S.D. 12)
(SP)$\bar{A}$ total QR	53 (17)	52 (17)	49 (16)
		3; t = 4.8; p < 0.01	
(SP)$\bar{A}$	85 (26)	86 (27)	76 (28)
		10; t = 3.3; p < 0.01	
$\frac{(SP)\bar{A}}{(SP)\bar{A}\ total\ Q}$	1.7	1.8	1.7

The usual response is attributed by Lamb and associates[5] to reflex vagal slowing when stretch receptors in the lung tissue or visceral pleura are stimulated. If this is the case, it is possible that those subjects who showed an increase in pulse rate may have reduced the stretch stimulus by closing the glottis and relaxing the inspiratory activity of the thoracic musculature, thus compressing the lung gases to a volume less than that of maximal inflation, whereas the others had maintained maximal inflation with the glottis open.

The duration of the Q-T interval is of some importance since it can be regarded as an approximate measure of mechanical ventricular systolic time, and its mean value in the present study was found to be unchanged with respiratory state at 0.36 second (Table I) in spite of the difference in heart rate. This constancy of Q-T for the individual at heart rates within the physiologic range was noted by Shipley and Hallaran[6] during sinus arrhythmia and confirmed by de Lalla and Brown[7] in subjects at the peaks of expiratory and inspiratory efforts.

With the increased length of cardiac cycle observed during breath holding at full inspiration it follows that the ratio $\frac{Q-T}{R-R}$ must decrease, but the reduction from 0.43 to 0.38 may not be wholly due to the decrease in heart rate per se, since when $\frac{Q-T}{R-R}$ is plotted against R-R there is some evidence to suggest that at a given cycle length the ratio is smaller during full inspiration than during full expiration.

In a previous study, it was shown that the QT of Bazett,[22] which was originally introduced to eliminate changes in Q-T with heart rate, was in fact different for the highly trained athlete as compared with the untrained subject. The present data indicate that it also varies with the respiratory state, and it would appear, therefore, that it fails to fulfill its purpose.

The primary reason for this investigation was to re-examine the theses that respiratory changes in the electrocardiographic record can be adequately explained by shift in cardiac anatomic axis alone or by varying hemodynamic conditions within the thorax or by a combination of both these factors.

The early observations of Einthoven, Fahr and de Waart[4] that the electrical axis of QRS became more vertical by approximately 20 degrees and that of T by 15 degrees in the change from expiration to inspiration were attributed solely to a corresponding change in cardiac anatomic position, but subsequently open

ion has tended to favor the view that this simple explanation is inadequate and that the electrical events in the heart are also affected by the interplay of respiratory and cardiovascular forces

The latest quantitative conventional lead studies on 38 male subjects by Simonson Nakagawa and Schmitt[1] appear to support the conclusion of Lamb that the changes are not due to a simple shift in anatomic position of the heart but are dependent on hemodynamic factors which result from variations in intrathoracic pressure at different phases of respiration Simonson and associates based *their contention on the* claim to have demonstrated a significant increase in spatial QRS T angle during inspiration which is *unlikely to occur as* a result of shift in cardiac position However the technique employed by those workers involved the use of RLF plane limb and standard chest leads which although hallowed by universal clinical acceptance are not sufficiently accurate especially in the anteroposterior axis for the determination of spatial vectorial angular values In addition the difference in spatial QRS-T angle of approximately 5 degrees between full expiration and inspiration given by Simonson is of doubtful statistical significance

The results for a preliminary determination of the RLF planar angles in the present study (Table II) show trends similar to those reported by Simonson and associates[11] except that both QRS and T vectors are more vertical by about 20 degrees at all phases of respiration This discrepancy may to some extent be attributable to the greater mean age (43 years) and very wide range in age (19 to 63 years) of Simonson s subjects since it has been shown that with increasing age both QRS and T vectors become more horizontal In this plane the QRS mean vector angles *increased* by *approximately* 15 degrees during breath holding at full inspiration and those subjects whose electrical axes were most *horizontal in expiration* showed the greatest angular increase The mean T vector angle was affected similarly so that the QRS-T angle in the RLF *plane remained constant*

In addition to their RLF plane data Simonson Nakagawa and Schmitt[11] determined the respiratory changes in vectorial angles using several of the current orthogonal vectorcardiographic techniques especially the SVEC III system of Schmitt and Simonson[12] This method employs vertical and horizontal lead electrode placements which in general are similar

Table VI Effect of breath holding on the lead field vector angles for the subsidiary group of 6 subjects

Subject		Frontal plane				Horizontal plane				Spatial QRS T
		QRS	T	QRS T	VG	QRS	T	QRS-T	VG	
A	Exp	6	56	+11	61	26	65	+39*	5	+41
	Insp	70*	54	+16	62	28*	71	+43	65	+48
B	Exp	149	47	+107	51	124	44	-80*	51	-71
	Insp	183	53	+132*	57	130	50	-100	56	-100
C	Exp	344	35	-51	19	338	1	+93	60	+93
	Insp	11	34	-3	23	347	81	+94	71	+94
D	Exp	13	71	-58	65	56	54	-2	55	+32
	Insp	47	9*	-3	7	40	61	+21	56	+29
E	Exp	63	66	-3	65	318*	54	+66	33	+35
	Insp	65	63	0*	65	344	51	+67	30	+33
F	Exp	55	71	-16	60*	299*	81	+14	351	+108
	Insp	60	80*	-20*	64	299	87	+118	4	+105

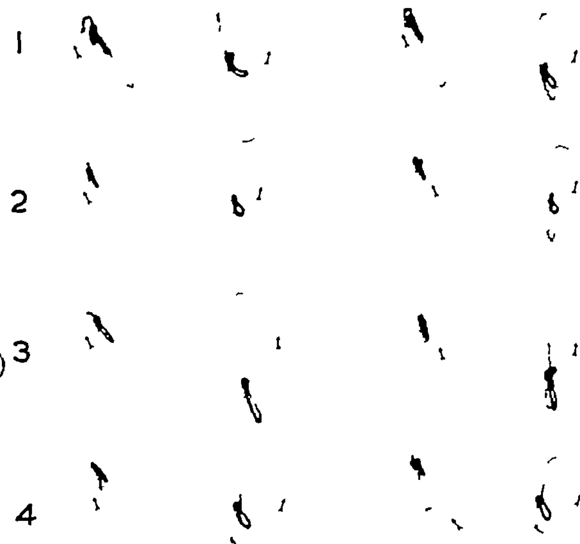


Fig. 1. Frontal and horizontal lead field planar loops for four typical subjects of the main homogeneous group.

to those of the lead field technique but the results recorded even in the frontal plane during normal quiet respiration differed markedly from those of the present study. The mean vector angles for 200 normal subjects[23] were 23 degrees for QRS and 26 degrees for T as compared with the 60 and 55 degrees respectively given in Table IV. However Pipberger[24] also using the SVEC III system more recently has established what he terms the "preliminary standards" for the method at 41 degrees for QRS and 44 degrees for T in the frontal plane which obviously approximate more closely those of the lead field system.

Similar differences in vector orientation are manifest by the two methods in the horizontal plane where the narrow HÂqrs-t of Schmitt and Simonson (36 degrees) is increased by Pipberger to 75 degrees and further to 133 degrees in our lead field study during normal respiration,* due to approximately equal displacements of QRS posteriorly and T anteriorly. The cor-

responding (SP) $\hat{A}_{QRS-T}$ values were 56 degrees (S D 19) according to Ball and Pipberger[31] and 102 degrees (S D 17) for our subjects

Although it is difficult to account for the divergent results of the two sets of investigators using the SVEC III method there are some obvious factors which could have contributed to the differences between the results given by that system and those of our lead field technique In the first place the average age of our subjects was about 17 years less than that of Pipberger's[34] and the method of lead weighting adopted in the SVEC III approach would have the effect of reducing the apparent spatial (and therefore horizontal planar) QRS T angle Furthermore to calculate their vector angles Ball and Pipberger[31] utilized the projections onto rectangular coordinates of the instantaneous deflection which bisected the spatial vector loop although it was recognized[34] that this procedure was open to serious criticism since it not only neglects entirely the total time occupied by the cardiac electrical activity but also assumes that the loop is inscribed symmetrically with respect to time The errors inherent in that method of computation are eliminated by using the voltage time units derived from algebraic summation of areas enclosed by scalar deflections from orthogonal leads as was done in the present study

Notwithstanding these quantitative differences between the SVEC III and lead field techniques it would have been anticipated that qualitatively similar vectorial trends would have been apparent as a result of varying the degree of pulmonary inflation Simonson and associates[14] claimed to have demonstrated in 22 male subjects a more significant mean increase of 16 degrees in (SP)$\hat{A}_{QRS-T}$ on full inspiration than was suggested by their RLF plane and chest lead analysis and they regarded this finding as conclusive evidence in favor of their thesis that factors other than purely anatomic ones were involved

The results presented in Table IV on the other hand do not support their conclusion that there is a significant alteration in spatial QRS-T angle with change in respiratory state although there were differences in the planar projections In the frontal plane both QRS and T vectors became more vertical on inspiration but T to a greater extent by 5 degrees so that it came to lie directly anterior to QRS as would occur if at the same time

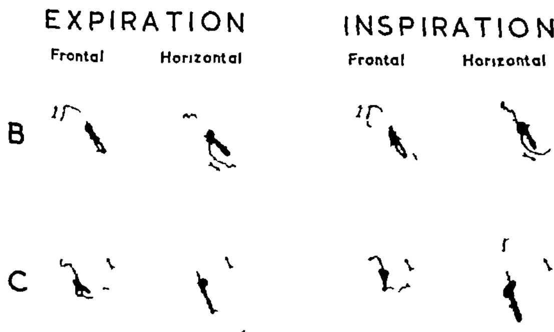


Fig 2 Frontal and horizontal lead field planar loops for two subjects (B and C) of the subsidiary

as the heart were rotating clockwise on an anteroposterior axis it also rotated anticlockwise (as viewed from below) around a hypothetical longitudinal axis directed downward and to the left. In the horizontal plane the mean direction of the QRS vector remained constant whereas the T vector became more anterior during full inspiration suggesting that the axis of longitudinal rotation was also directed posteriorly, i.e., it was more closely related *in space to QRS than to T.*

Thus interpretation of the vectorial spatial positional changes is supported by the alterations in the planar contours of the lead field vector loops with differing respiratory state as shown in Fig. 1. In the frontal plane the QRS loop is seen to become more vertically oriented and apparently rotated anticlockwise around a longitudinal axis at full inspiration.

In the particular experimental circumstances reported here, therefore, with supine subjects at the two extreme conditions of breath holding, the vectorial angular changes could be adequately explained simply by the assumption of a combination of anatomic rotations of the heart around anteroposterior and longitudinal axes.

Although there was no significant change in spatial magnitude of QRS (as conventionally determined by algebraic summation of deflections) there were reductions at full inspiration in "total QRS" (as previously defined[1]) and T magnitudes, principally due to decrease in voltage rather than in duration of activity.

It is already well known that the resistivity of lung tissue varies with the degree of its inflation, the specific resistance increasing with the content of air,[3, 22] but the extent of the increase in resistivity also depends on the frequency of the electrical signal[14] becoming progressively greater the lower the frequency.

Since the effect of inspiration on the spatial vectorial magnitudes in the present study was found to be more pronounced during the lower frequency repolarization component of the electrocardiogram, it suggests that this resistivity factor may be exerting an influence, although because the three orthogonal leads of the lead field system are likely to be affected equally, the spatial position of the vectors will be unaltered in spite of the changes in magnitudes.

So far consideration has only been given to the direct effects on the heart of changes in lung inflation, but indirect factors of cardiovascular origin may also theoretically be concerned. That pulmonary hemodynamic variation during the respiratory cycle modify the QRS complex has been demonstrated by Lamb,[14] and this modification may be due partly to the changes in *diastolic intracavitary blood mass* which result from fluctuating atrial filling pressures, with consequent variation in the electrical short circuiting effects described by Brody and discussed by Berwick and Jordan. In the more static respiratory conditions investigated here at the extremes of breath holding, however, there will be no rhythmic variation in atrial filling pressure, but it is possible that the end diastolic volume may be different in the two states of lung inflation and that this might have influenced the spatial position of the QRS vector. In fact, this position remained constant relative to T, and therefore the "Brody effect" appears to have been unimportant. The constancy in shape of the inspiratory and expiratory *spatial* QRS loops also suggests that there was no marked right sided or left sided overloading in either phase (see Cabrera and Gaxiola[12]).

Subsidiary group of 6 subjects. Of these 6 subjects whose unusual loop and vectorial patterns distinguished them from the main group, one (Subject F) differed only in respect to the configuration of his spatial QRS loop, which exhibited none of the usual early anteriorly directed electrical activity, but vectorially he showed exactly the same respiratory changes as the majority of subjects. At present, the only tentative interpretation that can be offered for this peculiarity is the possible existence in this heart of an uncommon time course for the early stages of depolarization which produced a loop contour resembling that of a relative physiologic *left sidedness.*

All of the other 5 subjects were characterized by anterior displacement of the QRS vectors to an extent which separated them statistically from the main group and was possibly due to some degree of relative right ventricular preponderance. On the other hand, it should be *noted that the*

orientation of T in these individuals did not differ significantly from that in the majority and therefore the vectorial pattern was not likely to be pathologic

Three of the 5 had spatial QRS-T angles which were not affected by changes in lung inflation and in all 5 there was the usual clockwise rotation about an antero-posterior axis but the position of the QRS and T vectors in the frontal plane suggested *clockwise* rotation at inspiration about a longitudinal axis i e opposite to that usually observed However inspection of their frontal plane QRS loops showed that those of Subjects A B and E were rotated *anticlockwise* from expiration to inspiration that of Subject C who had the most marked left axis deviation of all the 29 students examined was rotated *clockwise* whereas the result for Subject D was equivocal It would appear therefore that the hearts of these individuals with unusually anteriorly directed QRS vectors are also in general displaced anticlockwise anatomically around a longitudinal axis but that some unknown possibly hemodynamic factor complicated the apparent rotation as determined from the mean spatial vectors

Summary and conclusions

Twenty nine male medical students were examined by the lead field vectorcardiographic technique during breath holding at full expiration and full inspiration and the spatial vectorial results and planar loops were compared with those previously obtained during normal quiet respiration

For 27 out of 29 subjects the mean spatial QRS-T angle did not change with respiration although the majority showed marked clockwise rotation of frontal plane vectors and loops during inspiration with in addition evidence of anticlockwise rotation around a longitudinal axis directed downward to the left and posteriorly At inspiration the mean total QRS and T voltages were reduced

The significance of these findings is discussed in relation to the parts played in their causation by anatomic positional shifts in the heart and variation in hemodynamic conditions during the two states of breath holding

In the light of all the evidence it would seem most probable that the experimental data presented for these supine subjects can most simply and satisfactorily be explained on the assumption that the loop and vectorial changes are in most cases the direct results of the anatomic displacements of the heart at the extremes of breath holding

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On the normalization of the electrical orientation of the heart and the representation of electrical axis by means of an axis map

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Routine clinical electrocardiography currently includes the interpretation of 12 individual leads by trained readers. A variety of other methods of recording the electrical activity of the heart have been suggested. In general, each method has some desirable and some undesirable characteristics for cardiac diagnosis. For example, the vectorcardiogram reflects the time phase of voltages in various electrocardiographic leads. This advantage is obtained, however, at the expense of an adequate representation of other temporal relations. In a similar fashion, other recording methods each have characteristics which make some information more accessible and some less accessible than does the routine electrocardiogram.

The purpose of this report is to describe a method of electrocardiographic recording and analysis which provides information that is not easily accessible in other records of cardiac electrical activity. Limited clinical experience with the method will also be reported.

The method employs a lead system which provides the three mutually perpendicular components of the heart vector. These voltages are passed through a device ("resolver") which alters the lead system so that the relative orientation of the heart with respect to the lead axes is changed. This process can be considered as an effective rotation of the heart within the body. The resolver is adjusted to "rotate" the heart for both the QRS and T complexes so that in each case the mean axis of the heart vector points toward the left side and the plane of its motion is perpendicular to the long axis of the body. The original mean axis of the vector is then determined from the settings of the resolver knobs and plotted on a map along with the direction of motion of the vector. The voltages in the three new "normalized" leads are also recorded.

The information inherent in the three original electrocardiograms is thus separated into (1) a map which shows the mean axes of the QRS and T heart vectors as

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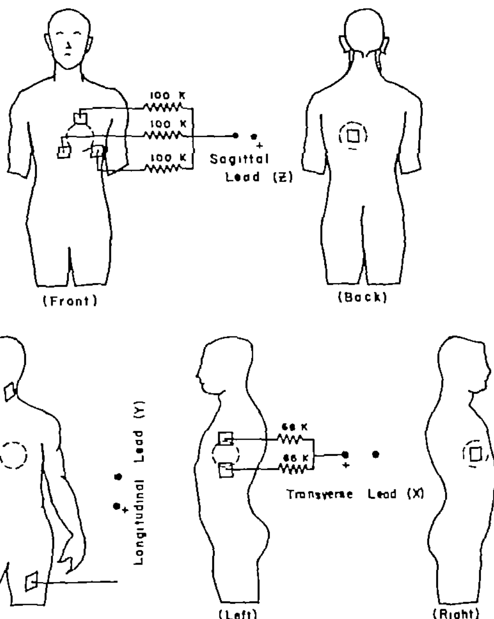


Fig. 1. Sketch of the orthogonal lead system employed in these studies. For further detail see Reference 8.

well as the plane of their motion; (2) two sets of three normalized electrocardiograms which reveal at a glance the maximum magnitude of the heart vectors, the extent of their sweep, and their planarity. The latter records are free from the effects of variation of the position of the heart within the body.

The method is essentially an extension of the Einthoven concept of electrical axis into three dimensions using relatively simple electronic instrumentation to determine the approximate mean axis of the QRS and the T. The method results in elimination of much of the normal variability of records from an orthogonal lead system.

Disadvantages of the method include the necessity for electronic equipment in addition to that employed in routine electrocardiography, and the time necessary to apply the technique.

Resolvers were first applied to electrocardiography by Schmitt. More versatile equipment which permitted rotation about each of the three axes of an orthogonal

lead system has been employed by Rijlant[3] and by Koechlin[2] and has been described by McFee and Parungao.[4] Clinical studies employing resolvers have also been reported by Milnor and associates.[5] Related but less flexible devices have been described by Brody[6] and by Pipberger. Rijlant has employed a resolver to obtain electrocardiographic leads which are similar in some respects to those obtained in this study; however, the present study also includes a specific display of the lead axis rotations necessary to obtain these leads.

Method of display and analysis

In the coordinate system used, the X axis (longitudinal) points toward the feet, the Y axis (transverse) toward the left side, and the Z axis (sagittal) toward the back. The XYZ voltages have been obtained with the axial lead system (Fig. 1) described in a previous publication.[6] Other orthogonal lead systems can also be employed.

The operation of resolvers may be viewed either as a rotation of the lead system about a fixed heart or as a rotation of the heart within a fixed lead system. Since rotations are relative, either view is equally valid. In this article the latter view is adopted.

With the method employed in these studies, the first resolver* rotation (θ) effectively turns the heart about the longitudinal (X) axis. If the θ knob is set to +90 degrees, a point formerly on the front of the heart next to the chest is moved around so that it is next to the left side. This angle can vary between plus and minus 180 degrees.

The second rotation (φ) turns the heart, already turned in effect about the longitudinal axis, about the sagittal axis ( ). Setting the φ knob to +90 degrees moves a point adjacent to the left side to a location next to the neck. The range of φ variation is limited to ±90 degrees.

The third and final rotation (ψ) turns the heart, already rotated about the longitudinal and sagittal axes, about the transverse (Y) axis. If the ψ knob is set to +90 degrees, a point on the front of the heart next to the chest is moved downward to the area facing the feet. The ψ angle can vary between plus and minus 180 degrees.

Through the use of a resolver, the heart can be effectively rotated into an orientation from which a more or less standard form of the electrocardiogram is obtained. This process is referred to here as "normalization." The specific procedure employed is the following one.

The θ knob is adjusted first so that the QRS deflection recorded from the Z output is equally positive and negative, with the principal deflection from the X output being positive. Adjustment of the φ knob is then carried out until the deflection from the Y output is also equiphasic. The ψ knob is then turned until the Y output is as small as possible, with the initial deflection of the Z output negative. These steps are repeated to insure proper adjustment. The QRS complexes in the new XYZ output are then recorded. The entire procedure is repeated for the T wave.

One result of this procedure is a three-lead electrocardiogram in which the QRS in the Z lead is biphasic, that in the Y lead is small and triphasic or quadriphasic, and the major QRS deflection in the X lead is prominent and positive. A similar set of records in which the T waves have the same characteristics are also obtained.

Another result is two sets of three angles, each representing the rotations about XYZ axes necessary to achieve the electrocardiographic patterns described.

To appreciate the geometric significance of the XYZ outputs and the angular rotations necessary to achieve these outputs, the heart may be visualized as surrounded by a spherical surface. Consider the sphere centered on the center of the heart and the heart vector by which cardiac electrical activity can be represented located at this center. If extended, this vector would pierce the surface of the sphere, and the location of this point would define the direction of the vector. For example, if the vector was directed straight up, its extension would pierce the top of the sphere. The position of the point at which the vector pierces the sphere may be shown on a two-dimensional map of the surface of the sphere in the same manner that the position of a city is indicated o

*Th[illegible] ... [illegible]
th[illegible] specified [illegible] Ref[illegible]

Fig. 2. Diagrammatic map of the direction of the heart vector during the QRS complex and the rotations necessary to achieve the normalized form of the complex. See text for detailed description of this figure.

a two-dimensional map of the surface of the world. The top of the map corresponds to that part of the sphere near the subject's head and the bottom of the map corresponds to the part of the sphere near the feet. The center of the map is taken to represent that part of the sphere near the center of the left side and its right and left edges correspond to the part of the sphere next to the line bisecting the right side. Lines corresponding to latitude and longitude on the sphere may also be shown on the map.

During the cardiac cycle the point representing the changing direction of the heart vector defines an arc on the map such as that labeled *A* in Fig. 2. This arc corresponds to the diagrammatic electrocardiographic lead voltages shown in the figure.

Rotation of the lead system about the Y axis through an angle θ so that the output of the Z lead is equally positive and negative moves the arc on the axis map to position *B* as shown in Fig. 2. A second rotation through the angle φ about the Z axis so that there is an equiphasic output from Y causes the arc on the axis map to move to position *C*. A final rotation about the X axis through the angle δ results in the smallest possible output of Y and moves the arc to position *D*. Changes in the appearance of the arc due to distortion by the map representation are not shown in Fig. 2.

Since in normal subjects the QRS and T axes are directed more or less toward the left side, the minimum rotation necessary to move the arc to this final position was obtained by taking the center of the map as the center of the left side of the body.

From the foregoing discussion the following points may be noted:

1. If the heart is considered to have been rotated in a fixed-electrode system, the cardiac vectors after normalization lie close to the horizontal plane with their approximate mean axis pointing toward the center of the left side. This means that the maximal deflection occurs in the output of the normalized X lead.

2. The approximate original directions of the mean axes of QRS and T are indicated by the settings of the θ and φ knobs. They may be plotted in the manner shown in Fig. 3. Such a diagram will be referred to here as an axis map. The inclination of the plane of the motion of the heart vector can also be shown on the axis map by

[illegible]

drawing an arrow on the map with an inclination equal to the setting of the δ knob If δ is positive the arrow points downward and if negative it points upward

3 The peak deflection in the normalized X lead usually represents the maximal magnitude of the heart vector

4 Deviations of the heart vector from a plane are reflected by the amplitude of deflections in the normalized Y lead If no deflections occur in this lead it indicates that the heart vector is confined to a single plane during the portion of the cardiac cycle being investigated

5 The ratio of the amplitude of deflection in the normalized Z lead to that of the X lead reflects the range of the angular sweep of the heart vector during the portion of the cardiac cycle being studied

6 The area of the spatial loop is approximately proportional to the product of the peak to peak amplitudes in the normalized lead X and Z For an elliptical loop this area is $\left(\frac{\pi}{4}\right)$ (X peak to peak) (Z peak to peak) This area is equal to the magnitude of Burger's polar vector After normalization the polar vector points toward the head (considering the heart to be rotated in a fixed-electrode system) The direction of the polar vector before rotation can be determined from θ φ and δ using either a set of equations or a special nomograph

Clinical observations

The method described was applied to 29 normal subjects and 26 patients whose electrocardiograms showed a variety of ab

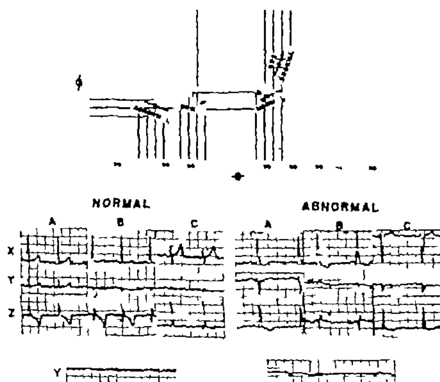


Fig 3 Representative normal and abnormal record The XYZ lead of each subject are labeled A Record of normalized QRS complexes are shown under B and record of the normalized T waves under C normalized QRS complexes in lead Y recorded at higher paper speed (50 mm sec) are also shown The approximate mean directions of the heart vector during the QRS and T interval are shown as black dots on the map These directions are obtained from the settings on the resolver dial after the electrocardiograms have been normalized The inclination of the plane of motion of the heart vector is shown by the arrow through these dots

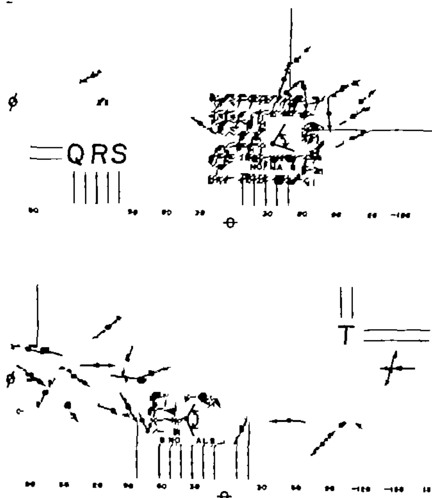


Fig 4 These are axis maps of the approximate mean axes of the QRS complex and T wave as determined by the rotations necessary to achieve the normalized form of the electrocardiogram Axes from 29 normal records fell within the shaded areas and had range of inclination as shown by the insert in these areas In 26 subjects whose conventional electrocardiograms were abnormal the approximate mean axis of either the QRS or the T or of both fell outside the normal range In this figure all the approximate mean QRS and T axes which were located outside the normal area are shown

normalities The latter included nonspecific S T segment and T wave abnormalities evidence of myocardial infarction left and right ventricular enlargement and right and left bundle branch block

Both normal and abnormal records exhibited variability in the amplitude of the heart vector as well as its angular sweep Normalized records from some subjects with abnormal conventional electrocardiograms could not be differentiated from those of some normal subjects It appeared however that there was greater variability in the entire group of normalized records from abnormal subjects When quantitative normal standards have been established and individual abnormalities are investigated it is possible that some of the parameters accessible in the normalized records will be clinically useful

The axis maps provided an almost complete separation of the groups classified as normal and abnormal on the basis of the conventional electrocardiogram All mean QRS and T axes from the normal group fell within the shaded areas shown in Fig 4 Individual QRS and T axes from the patients whose conventional electrocardiograms were abnormal are also shown in this figure Either the QRS or T axes

or both axes of all of these patients were located outside the area occupied by normal axes on the axis map These findings indicate that much of the electrocardiographic information on which a separation into normal and abnormal groups is made by routine interpretation is reflected by the mean axis of QRS and/or T waves

Since a variety of electrocardiographic abnormalities were represented in the abnormal group and there were only small numbers of each specific abnormality a definition of the characteristics of individual abnormalities in the axis maps and the resolved leads was not attempted For this type of study larger numbers of records of individual abnormalities will be necessary It is not unlikely that clinically useful correlations will eventually be found between some of these abnormalities and unusual characteristics of the amplitude sweep and planarity of the heart vector as shown by the normalized electrocardiograms

Discussion

The method of analysis and display described reduces the variability of a set of orthogonal leads to a minimum When the normalized XYZ records from patients with abnormal cardiac electrical activity fall within the range of variability of normalized records from normal subjects the abnormalities are reflected by the axis map Quantitative description of the range of normal variability in the axis maps is so simple that abnormalities reflected in the maps may be readily recognized

The major finding of the present study was that normal records and a group of miscellaneous electrocardiographic abnormalities could be separated by the axis maps This constitutes an approach to machine interpretation of the electrocardiogram since the only element of interpretation in the technique was that of matching Y and Z leads to a predetermined pattern by adjusting the resolver knobs

The display of normalized XYZ leads also has several other characteristics of interest The degree of nonplanarity of cardiac electrical events is presented in quantitative terms The approximate magnitude and orientation of the polar vector the angular sweep of the heart vector and the maximal magnitude of the QRS and T vectors may be easily determined from the normalized leads Any or all of these parameters may have clinical usefulness in the recognition of specific abnormalities of the electrical activity of the heart Further study of larger numbers of records will be necessary to evaluate this possibility

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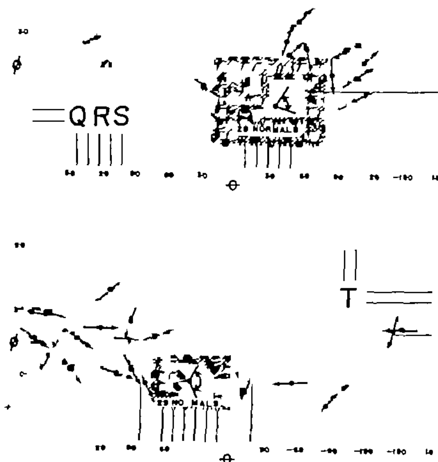


Fig 4 These are axis maps of the pproximate mean es of the QRS complex and T w e as determined by the rotations necessary to achieve the normalized form of the electrocardiogram Axes from 29 normal records fell within the haded areas and had a range of inclination as shown by the insert in these areas I 26 subjects whose conventional electrocardiograms were abnormal the ap proximate mean axis of either the QRS or the T or of both fell outside the normal range I this figure all the pproximat mean QRS and T axes which were located outside the normal area are how

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This in turn would require new values for the coefficients. In the S system each component of the vector is determined by one angle lead. Consequently we have chosen to adapt the S system to the B system and not the reverse. This does not mean however that we attribute the difference of these two systems to an error in S only.

Method and material

In the Schmitt system there is no mention of scale so that we have chosen the sensitivity in such a manner that the sizes of the loops in the S and B systems were on the average approximately equal. The frontal and horizontal projections in each system were photographed simultaneously.

The agreement between the frontal projections of the two systems is satisfactory; the main discrepancy is in the horizontal projection and is the consequence of the uncertainty in the determination of the sagittal component of the heart vector caused by the relatively small dimensions of the human thorax in the sagittal direction.

It appeared that in the S system a footward loop generally is directed more posteriorly than in the B system. This was expressed previously[4] in an analytical form by the relation

$$Z = -0.2\,X_B + 0.6\,Y_B + 0.9\,Z_B$$

in which Z_S is the sagittal component of the vector in the S system and X_B, Y_B and Z_B are the components in the B system. Because of the contribution of the Y term which is positive for points of the vector loop below the zero point, Z will become proportionately greater than Z_B at points which are increasingly distant from the zero point moving in a caudal direction.

The sagittal component in the S system is exclusively determined by and proportional to the voltage between its dorsal and precordial electrodes. Consequently the desired change in this component might be attempted by shifting these two electrodes. The anatomic axis connecting these electrodes changes therefore in position; we choose to call this axis the pick-off axis. If the dorsal electrode is displaced cranially and the precordial electrode caudally an inclination of the sagittal pick-off axis is effected. This will bring about a decrease in the magnitude of the projection on the axis of a caudo posteriorly directed vector and an increase in the case of a caudo anteriorly directed vector. The net result would be a rotation of the vector loop in the ventral direction over a certain angle (see Fig. 1). This reasoning would only be fully justified if image space and anatomic space were considered to be identical, which is certainly not true. Preliminary investigations however have supported the above mentioned displacement of electrodes; the distance was empirically established at 6 cm for each electrode.

Our material comprised 64 normal individuals and 86 cardiac patients. Comparisons were made by three observers independently by grading the agreement between the horizontal projections of the loops according to a scale ranging from 0 to 10. A score of 10 indicated as perfect an agreement as could be expected to exist within one system between different heart beats of the same subject[1,3]. An example of the improvement in agreement between systems B and S is shown in Fig. 2.

Results and conclusions

From the group material the average of the scores obtained from the comparison

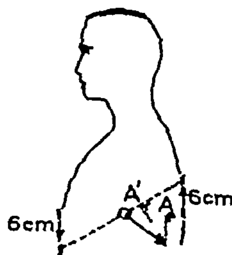


Fig. 1. OA represents the projection of the heart vector on the pick-off axis before and OA' after displacement of the electrodes. It can readily be seen that OA' < OA for posteriorly directed vector.

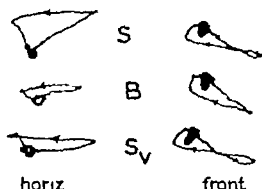


Fig. 2. S_V, the loop obtained after displacement of the electrodes, shows better resemblance to B in the horizontal projection than does S.

between B and the original S and its variant S_V, respectively, revealed a value of 6.0 ± 0.12 for B-S and 6.5 ± 0.12 for B-S_V. The average of the individual differences between B-S and B-S_V was 0.5 ± 0.07. This difference is statistically significant, but the improvement is hardly large enough to render the method worth while for practical use in its present form. The failure of this result to fulfill our expectations may be attributed to (1) the application of a rotation instead of a shear, which would be required considering the above-mentioned formula for Z_s; (2) the assumption that the discrepancies between S and B are due to a difference in the sagittal components only and can be remedied by changing these components only; (3) the assumption that image space and anatomic space are identical.

Therefore, we have abandoned this method and have turned our attention to the procedure of changing the coefficients.

Summary

An attempt was made to improve the agreement between the Schmitt SVEC II and the Burger B_1W_4 systems by shifting the ventral and dorsal electrodes of the SVEC II system caudally and cranially, respectively. Although a statistically significant improvement in agreement was obtained, it hardly warrants practical use of the procedure.

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Effect of tilting on RK time in normal subjects and in patients with heart disease

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Experiments in our laboratories[1] have demonstrated that the time lag from a reference point on the QRS complex of the electrocardiogram (Q or R) to the onset of aortic ejection (F) becomes shorter as the stroke output increases. The velocity of arterial transmission of the pulse wave is not affected by these changes in output. Thus, variations in stroke output may affect the arrival time of the pulse wave at the brachial artery.

During a given beat, the arterial sound begins as the pulse pressure rises to and then exceeds the cuff pressure. We have utilized the arterial sounds to represent the time of arrival of the pulse wave at a given cuff pressure. A reference electrocardiogram recorded with the sound permits measurement of the electromechanical lag. The sensitivity of this method is shown by the fact that the time from the midpoint of the upstroke of the R wave of the electrocardiogram to the onset of the arterial sounds of Korotkoff (K) at a given cuff pressure level is shortened consistently by procedures which increase stroke output, such as general exercise or the administration of epinephrine or norepinephrine.[2] The possibility was therefore suggested that RK time may provide a clinical assay of changes in stroke volume.

Postural changes are known to affect the venous return and thereby to modify the stroke volume. The purpose of the present study was to evaluate the cardiodynamic effects on the RK time induced by postural changes in normal subjects and in patients with congestive heart failure. An electronic instrument designed and constructed in this laboratory was used to record the arrival time of the arterial sounds at various arterial pressures.

Materials and methods

Studies were carried out on 14 normal subjects and 17 patients. The brachial arterial sounds during routine measurement of blood pressure were picked up by a microphone which was held firmly to the skin by a suction cup. The arterial vibrations were inscribed on a cathode ray oscilloscope, each horizontal sweep was triggered at a selected isovoltage level near the peak of the R wave of the electrocardiogram. The R wave was used since this large wave was more effective in triggering

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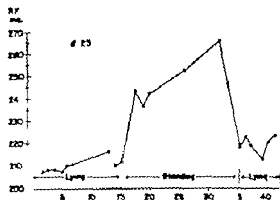


Fig 1 Data obtained in successive readings on 25 year-old healthy male Vertical scale gives the time from onset of R wave to onset of arterial sound when cuff pressure is at diastolic pressure levels (RK$_D$) Horizontal scale is time in minutes Each dot represent single measurement The first 11 dot represent a normal variation of about ± 5 msec around an average of 212 msec The next 4 dots represent the change while the subject is standing passively RK is prolonged at once to 235 msec and increases gradually to 265 msec Immediately on passive return of the subject to the lying position the RK$_D$ shortens to about 220 msec Discussed in text

the sweep than the smaller Q wave Tests showed that the difference between the onset of the Q and the point of triggering on the R wave was about 30 milliseconds (msec) In each case this value was determined from the electrocardiogram

The tracing was photographed with a Polaroid camera and the interval from the upstroke of the R wave of the electrocardiogram to the onset of the sound was measured on the finished record Time and calibration pulses introduced into the record permitted measurement of onset of the sounds to within 5 msec By varying the delay time between the activation of the R wave triggering circuit and the onset of the sweep we were able to make several recordings on each film

Four to 10 records were obtained in each experiment as the patient lay supine on a tilt table A similar series was made after the patient was passively changed to the 75-degree upright position and again after return to the horizontal

Results

1 Reclining subjects at rest In 11 normal subjects the average RK time at diastolic pressure levels (RK$_D$ time) was 207 msec ranging from 191 to 242 msec in accord with previous findings

In 8 patients with previous or present congestive failure the RK$_D$ times averaged 198 msec varying from 146 to 236 msec Thus RK$_D$ did not assist in differentiating the patients with failure from the normal subjects

2 Effect of postural change

A NORMAL SUBJECTS Fig 1 shows a serial record of RK$_D$ times during postural changes in a normal subject When the subject was in the supine position RK$_D$ varied from 207 to 217 msec with an average of 211 msec After the subject was moved into the standing position the RK$_D$ was significantly prolonged by 30 msec or more Return of the subject to the supine position shortened RK$_D$ to approximately the control level (Table I) Similar results were obtained in all of 14 normal subjects tested (Fig 2)

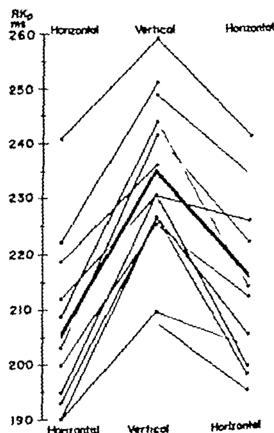


Fig 2 Averages of data on effect of posture in each normal subject (light lines) and in the entire group (heavy line) as the position was changed The average increase in RK time was 30 msec with incomplete recovery on return to the horizontal

Table I. Average changes in RK_D time

Postural change	14 Normal subjects	8 Patients with congestive heart failure
Horizontal to vertical	+35 msec	+6 msec
Vertical to horizontal	−19 msec	+12 msec

+Prolongation; −shortening.

B. PATIENTS WITH PREVIOUS OR PRESENT CONGESTIVE HEART FAILURE. In the cardiac patient the prolongation of the RK_D time when he was standing and the shortening after he was returned to the horizontal position were less marked than in the normal subject (Table I). In some tests RK_D in the cardiac patients showed a reversal of the normal response. RK_D was slightly shortened after the patient had assumed the upright position and slightly prolonged after he was returned to the horizontal position (Fig. 3).

3. Effect of an antigravity G suit. To eliminate the gravitational tendency of blood to pool during passive standing, postural tests were carried out in 5 normal subjects wearing an Air Force antigravity suit inflated to 260 mm. Hg (Table II). The antigravity suit consisted of nylon trousers arranged so that air bladders compressed the calves, thighs, and abdomen of the subject. Fig. 4 shows that while the suit was inflated, the RK_D changed only slightly when the subject assumed the standing position. When the air pressure in the suit was then dropped to atmospheric levels, a significant prolongation of the RK_D time by as much as 47 msec. occurred.

In the present experiments the diastolic pressure remained relatively constant during the postural changes. It rose an average of 2 mm. Hg when the subject was standing and fell an average of 3 mm. Hg when he resumed the supine position. These slight changes in diastolic pressure did not correlate with the RK_D time.

Discussion

The normal heart responds to an increase or decrease in venous return with similar variations in the stroke output. The heart in failure, on the other hand, may be unable to maintain this performance.

Normal subjects showed a significant prolongation of RK_D time when they assumed the erect position and a shortening of this time when they returned to the horizontal position. It is generally appreciated that change of position shifts a significant volume of blood to the dependent portions of the body. The transitory reduction in the venous return to the heart on assumption of the upright position can thus be expected to produce a fall in cardiac stroke and minute output.[8,9] The compensatory vasoconstriction which maintains the systemic blood pressure cannot affect this deviation of blood volume to the venous system. Sustained inflation of the antigravity suit counterbalances the gravitational tendency for venous pooling and thereby reduces the effects of assumption of the upright position. Our data showing a prolongation of the RK_D time on passive standing, which is inhibited by a G suit

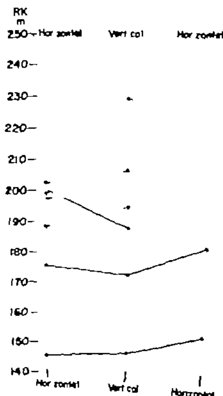


Fig. 3. Effect of changes in posture on RK in patients with heart failure. Conventions as in Fig. 2. Each dashed line represents average data on one patient with previous heart failure. Each solid line represents average data on patient ... present failure. The heavy bar is the ... entire series.

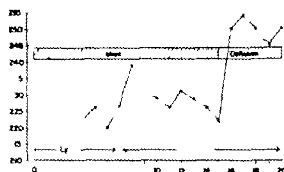


Fig. 4. Effect of G suit on postural changes in RK_D time. The number of the trial is given on the horizontal scale. Inflation prevented the expected prolongation of RK_D time when the subject was moved to the upright position. When the G suit was deflated, the RK_D time was prolonged by about 30 msec. Discussed in text.

are consistent with the expected changes in stroke volume.

RK_D time may be subdivided into two functional intervals: (1) the RE interval from R of the electrocardiogram to the onset of ejection (E), and (2) the EK interval, i.e., the time for transmission of the pulse wave from the aortic valve to the point of production of the arterial sounds.

Since the time for transmission of the pulse wave at a given diastolic pressure appears to be unaffected by changes in position of the body, the variations of the RK_D time which we observed must be considered as being due to changes in the pre-ejection (RE) time. Recent studies on animals in this laboratory have demonstrated that at constant diastolic pressure the RE time shortens as the stroke volume is increased, whereas the pulse wave velocity (EK) remains unchanged. It may then be suggested that variations in the RK_D time during specific interventions such as tilting may be utilized clinically to appraise changes in stroke volume. A shortening of RK_D may thus indicate an increase in stroke volume, whereas prolongation may represent a decrease in stroke volume.

The stroke output of patients with congestive heart failure remains relatively unchanged despite exercise or the intravenous infusion of fluids.[11,14] The diminished response of the RE time to the postural change may reflect a limitation in stroke output in cardiac patients. Wiggers' intraventricular pressure curves[1] demonstrated that after infusion of saline the isometric pressure upstroke became steeper and the isometric contraction period was shortened. After excessive infusion and the development of cardiac failure, as evidenced by a diminishing contractile power, the steepness of the upstroke decreased and the isometric contraction time was prolonged.

We may assume that the increase in venous return after the subject has taken the horizontal position, and the decrease when he is standing, should similarly affect the steepness and duration of the rise in intraventricular pressure. However, this effect was not seen in the patients with failure. Dysfunction of the myocardium may thus be reflected in the patterns of modification of the RK_D time after postural changes.

Table II. Effect of G suit on postural change

Age (yr.)	Without G suit			With G suit		
	Lying (msec.)	Standing (msec.)	Difference (msec.)	Lying (msec.)	Standing (msec.)	Difference (msec.)
21	220	237	17	231	230	−1
44	191	211	20	204	204	0
27	201	227	26	162	168	6
[illegible]	204	247	43	224	229	5
39	191	228	37	224	218	−6
Average	201	230	29	209	210	1

All subjects were males.

These data suggest that recordings of arrival time of the pulse wave during a given cardiac cycle may provide significant information concerning cardiovascular status. The simplicity of our method permits recurrent clinical assays of changes in cardiac function during physiologic and therapeutic studies.

Summary

The time from onset of the R wave of the electrocardiogram to the registration of the arterial compression sound of Korotkoff at diastolic pressure level (RK_D time) was measured before and after passive changes in posture. In normal subjects the RK_D time was significantly prolonged after they assumed the upright position and shortened to control values when they returned to the horizontal position. These effects were diminished by compression of the calves, thighs, and abdomen of the subject with an antigravity suit.

In patients with previous or present congestive heart failure the response of the RK_D time to the changes in posture was significantly reduced or was opposite to that seen in normal subjects.

These data may be interpreted to suggest that in normal subjects with a relatively constant level of diastolic pressure, RK_D time varies inversely with the stroke volume. This relationship is eliminated in patients with congestive failure. The simplicity of the method permits the study of responses to experimental or therapeutic procedures.

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Case report

Anomalous coronary artery connecting with the right ventricle associated with pulmonary stenosis and atrial septal defect

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Congenital abnormalities of the coronary arterial system are becoming of greater importance since surgical treatment is possible. Preoperative diagnosis is therefore of paramount importance. Diagnosis should include the type of abnormality, the presence of associated defects, and the type of hemodynamic disturbance produced. One group of coronary arterial malformations is of purely academic interest since no functional disorders arise from them; quite often they are found at autopsy. Such is the case with a single coronary artery, both coronary arteries arising from the same aortic sinus, some of the distribution abnormalities, etc. There is another group of malformations the importance of which is evident inasmuch as they represent abnormal left to right shunts. Such is the abnormal connection of one coronary artery with one of the cardiac chambers (right auricle, coronary sinus, right ventricle) or with the pulmonary artery, thus establishing a shunt between systemic and pulmonary circuits. Sometimes the connection is made with the left cardiac chambers giving rise to an arterial systemic shunt. Edwards and Burchell reviewed the subject of the anomalous origin of the coronary artery from the pulmonary artery and suggested the possibility of ligating the abnormal coronary vessel since hemodynamically this condition acts as an arteriovenous fistula. Six patients with such a condition have been operated upon to date.[1,2]

On occasion, combinations of coronary arterial abnormalities lead to complex malformations which are difficult to diagnose and treat. The case which will be presented illustrates this situation inasmuch as there was a single coronary artery with abnormal distribution and abnormal situation, one the branches of which connected with the cavity of the right ventricle. This condition was associated with a trilogy of Fallot (atrial septal defect plus pulmonary valvular stenosis).

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Fig 1A Frontal view Slight cardiomegaly Straight middle segment and normal hilar vessels Peripheral vascularity is decreased

Description of case

L R L was a 6-year-old boy who had been born of an uncomplicated pregnancy and normal delivery. A congenital heart condition had been recognized when he was 1 month of age. He remained asymptomatic until he was 3 years old at which time easy fatigability was noticed. Cyanosis was present when he was examined but it had not been apparent to the mother for which reason the time of its appearance remains unknown. Physical examination in December 1959 disclosed a poorly developed cyanotic child who was 108 centimeters in height and weighed 17 700 kilograms. Clubbing of the fingers and toes was evident. The apex of the heart was felt at the fifth left intercostal space in the mid-clavicular line. A systolic thrill was felt at the third and fourth left intercostal spaces. At this site there was a harsh holosystolic murmur Grade 3/4 which extended toward the base especially under the left clavicle. There was soft superficial diastolic murmur at the mid precordial area extending somewhat to the apex. The second pulmonary sound was of decreased intensity and pure.

On x-ray examination the heart in the frontal view (Fig 1A) appeared to be slightly increased in size. The pulmonary segment was straight the hilar vessels were normal and the periphery of the lungs were overly transparent.

The electrocardiogram (Fig 1B) suggested right auricular enlargement and right ventricular hypertrophy.

The child was thought to have tetralogy of Fallot associated with some other anomaly responsible for the diastolic murmur. It was suspected that a coronary vessel connected with one of the right cardiac chambers or that there might be an added aortic regurgitation.

A conventional catheterization demonstrated an atrial septal defect with right-to-left shunt (Table I). There was a large gradient of 91 mm Hg across the pulmonary valve and the graphic registration of the pressures indicated a valvular type of pulmonic stenosis. The difference in pressure between the ventricles eliminated the idea of an intact ventricular septum.

An angiocardiogram (Fig 2) was made with a No 8 Lehman catheter injecting 3 cc of 70 per cent Reopak directly into the right ventricle. Plates were taken in the posteroanterior and left lateral views. The right ventricle was seen to have hypertrophic wall, marked trabeculation and increased thickness of the crista supraventricularis. A dome shaped valve was outlined and the eccentric jet which emerged from it was readily visible during systole. Throughout the first second a round shaped image (frontal view) began to appear near the apex of the right ventricle; this image was continued by a tortuous path vessel of irregular caliber which ascended parallel to the outflow tract of the right ventricle (Fig 2A). In the lateral plane (Fig 2B) this structure could be seen to lie on the anterior border of the cardiac contour. The levoangiocardiogram (Fig 2C) showed that this vessel emerged from the aorta immediately above the level of the aortic valve. We concluded that this was an anomalous connection of a coronary artery with the right ventricle associated with trilogy of Fallot.

An interesting feature of this case was that during systole the right ventricle pumped blood through the anomalous coronary vessel into the aorta and during diastole blood regurgitated from the aorta into the right ventricle.

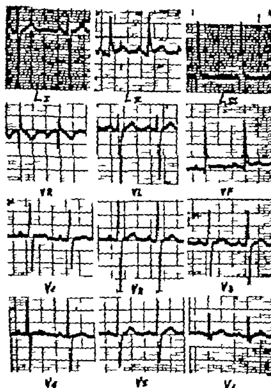


Fig 1B The electrocardiogram shows right axis deviation and RS complexes with positive T waves in Lead V. The tracing is suggestive of right ventricular enlargement.

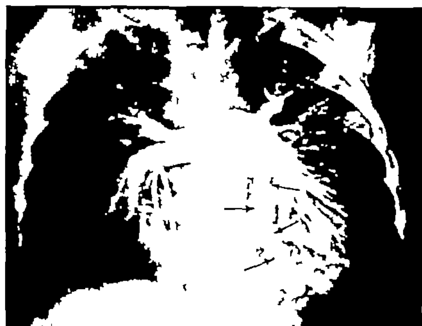


Fig. 2 1 Angiocardiogram in the frontal plane. The inflow tract of the right ventricle and the pulmonary artery are filled with opaque substance. The arrows point out the path of the abnormal coronary artery.

The patient underwent operation in May 1960. When the pericardium was opened the surgeon visualized the dilated and tortuous coronary vessel which connected with the right ventricle entering the ventricular cavity at the lower third of its anterior aspect where it formed an aneurysmal dilatation. A thrill was *felt over the entire length of the vessel*. A clamp was placed on this coronary artery about 4 cm from its origin at the aorta. Since no electrocardiographic abnormalities appeared the vessel was interrupted. The valvular pulmonic stenosis was then treated by means of the open heart technique. A markedly stenosed valve was found. The crista supra ventricularis was partially resected in order to widen the infundibulum. When the heart was closed *cardiac standstill occurred. The heart* was massaged and it recovered but within an hour a second standstill took place and the heart never recovered again despite resuscitative measures.

Autopsy report. The heart weighed 115 grams. The anterior aspect of the right ventricle showed a ventriculotomy incision which was about 4 cm in length. The anterior descending coronary artery was sectioned in its middle part 4 cm distant from its *origin. An atrial septal defect was seen when the* heart was opened. The right ventricle showed the partially resected crista supra ventricularis. Its cavity was moderately dilated and its wall was hypertrophic. The pulmonary sigmoid valve cusps were thickened and they showed surgical disruption (Fig. 3 1). A single coronary artery was found emerging from the right anterior sinus of Valsalva of the aortic valve (Fig. *3B*). The ostium of this vessel measured *0.6 cm in diameter. The path followed by* the vessel was directed downward forward and to the left. It gave off some branches about 3 cm from its origin. It proceeded along the anterior interventricular sulcus showing a changing caliber which varied between 15 and 20 mm in circumference. It opened into the right ventricular cavity at the level of the inferior and anterior third of the interventricular *septum where it had made a tunnel of irregular* shape lined with endothelium and showed numerous small holes of different sizes corresponding to many finer vessels. The opening was located at the trabecular zone.

Injection of the coronary network through the ostium of the single coronary artery with the technique described by Schlesinger (modified by Reiner and associates[9]) demonstrated the filling of the *artery of two large branches and of several smaller* twigs which spread through both ventricles in the fashion of an extensive collateral network (Fig. 4 1). The different branches of the abnormal coronary artery arose from the main vessel at very obtuse angles in the distal sense (Fig. *4B*) in contrast with the normal pattern.

Discussion

Abnormal connection between a coronary artery and one of the cardiac chambers is an unusual malformation only 52 instances have been reported to date in the literature. In 16 of these operation was successfully carried out[4,1] and in 2 (Bosher and associates case[13] and ours) *death occurred postoperatively*. In only 3 of the cases in which operation was performed were there associated malforma

The autopsy was performed by Dr. E. Perr



Fig. 2B In the lateral plane the prominence of the crista supraventricularis is visible. Notice the dome shaped stenotic pulmonary valve. There is slight poststenotic dilatation of the pulmonary artery. Notice the path of the anomalous coronary artery at the anterior border of the cardiac contour pointed out by the arrow.



Fig. 2C The levoangiocardiogram shows the abnormal coronary vessel (pointed out by the arrow) arising from the aorta and reopacifying the right ventricle after an anterior course.

Table I

	Gas analysis		*Pressures (mm Hg)*		
	Vol ( )	*Saturation* ( )	*Systolic*	*Diastolic*	*Mean*
IVC	12 56	60	—	—	—
RA	12 66	61	—	—	2 5
RV	11 40	55	105	−7/0	52 5
PA	9 12	44	14	—	7 5
WP	—	—	—	—	2 5
LA	14 57	70	—	—	2 5
LV	1 50	72	77 5	2 /5	37 5
FA	15 56	76	—	—	—

Oxygen capacity 20 49)
Hemoglobin 15 29 Gm
Oxygen consumption 173 /min
Pulmonary flow 1 374 L /min
Systemic flow 5 760 L /min
Right to-left shunt 3 386 L /min

IVC Infer vena cava RA Right atrium RV Right ventricl PA Pulm nary artery WP W dg pressure LA Left atrium LV Left tricle FA Fem al tery

tions both the case of Bosher[1] and that of Sondergaard were complicated by patent ductus arteriosus and ours was complicated by trilogy of Fallot

Up to 1950 only 42 cases of single coronary artery had been reported (Smith) Smith divides these cases into three groups according to the distribution of the single vessel Our case belongs to his Group III that is a case in which it is impossible to differentiate two coronary branches right and left A single coronary artery is often a postmortem finding without there having been any previous clinical symptomatology In our case symptoms and signs depended upon the abnormal connection of the single coronary artery with the right ventricle and also upon the presence of added malformations

Blakeway[1] and Edwards described a rare type of abnormality of the coronary artery associated with atresia of the pulmonary valve intact interventricular septum and normal homologous atrioventricular valve The abnormal coronary vessel in such instances originates from several small blood channels in the right ventricle In this respect we share the view of Williams and associates[1] who believe that from an early embryonic stage the presence of a valvular barrier at the pulmonary area forces the blood from the right ventricular cavity through the intertrabecular sinusoids causing them to persist in an abnormal fashion Later these channels coalesce and form a large vessel which communicates with the coronary system In our case a similar mechanism may be postulated although atresia of the pulmonary valve was not present however stenosis of this structure was severe This could very well have forced the blood to flow through the abnormal vessel in a right to left direction this situation might also have been responsible for the presence of multiple smaller vessels which originated from the common vessel leading from the right ventricle into the coronary artery through the thickness of the right ventricular wall

In so far as we are able to ascertain this case is the only one of its kind in which a complex malformation of the coronary arteries is associated with a trilogy of Fallot

Marked cyanosis and important desaturation of peripheral arterial blood could easily be accounted for by the right to left shunt present at the atrial level However right ventricular pressure was higher than systemic pressure and filling of the abnormal coronary vessel from the right ventricle as demonstrated by the angiocardiogram makes it quite likely that part of the right to left shunt could be effected through this path although blood gas analysis did not substantiate this assumption

Because right ventricular systolic pressure was higher than aortic systolic pressure we may assume that a good portion of the right ventricle and probably of the left ventricle received venous blood durin systolic ejection of the right ventricle through the abnormal coronary vessel However it must be mentioned that no clinical or electrocardiographic signs indicated myocardial ischemia This fact is not wholly surprising since the right ventricle seems to withstand anoxia much better than does the left ventricle

Furthermore it is a well known fact that patients in whom the right coronary



Fig. 37. The infundibulum and the pulmonary artery has been opened to show the pulmonary valve and the crista supraventricularis. Notice the valvotomy and the partial resection of the crista.

artery emerges from the pulmonary artery have better tolerance and outlook than patients in whom the left coronary artery arises from the pulmonary artery. In the latter case there are clinical and electrocardiographic evidences of coronary insufficiency. The former patients usually have a normal myocardium, whereas the latter usually show myocardial changes of the type commonly described in myocardial infarction after coronary occlusion of sclerotic origin. Authors who are well versed on the subject agree that the most important factor for ischemia is the low perfusion pressure of the coronary arteries and not the low content of oxygen in the blood, as proved by the absence of such ischemic manifestations in severely cyanotic patients with congenital heart malformations in whom despite a very low content of oxygen in the blood which supplies the myocardium there are no ischemic manifestations. In our case the markedly elevated right ventricular pressure was able to maintain a good perfusion pressure of the coronary arterial system.

The diagnosis of the anomalous connection of the coronary artery with the right ventricle is difficult to establish. Up to the present time only [illegible] patients have been suspected preoperatively of having this malformation. A great number of the other cases reported have been diagnosed variously as patent ductus arteriosus or as ruptured aneurysm of a sinus of Valsalva into one of the right cardiac chambers. These diagnoses have been due in all likelihood to the frequent presence of a continuous murmur (machinery type) or a systolic-diastolic murmur at different areas of the precordium. In the case of an anomalous coronary artery of the type under discussion there are some features which might lead to the correct diagnosis. Such are the atypical location of the murmur usually at a very low portion of the precordium, the superficiality of the auscultatory phenomenon which we find quite suggestive, and finally the



Fig. 38. Notice the catheter introduced into the ostium of the right coronary artery, which rises from the right anterior sinus of Valsalva.



Fig 4A Postmortem injection of the coronary net work Injection of the opaque substance at a greater pressure at the proximal end of the coronary artery at the level of the single ostium Notice the two important branches arising from the main vessel which supply the entire left ventricle and part of the right ventricle giving off numerous collateral vessels which anastomose profusely

diastolic component of the continuous or systolic-diastolic murmur which is considerably louder than the systolic component

Our patient had a double murmur which was heard over practically all of the precordial area The systolic component was louder at the pulmonary area probably because of the presence of pulmonary valvular stenosis This finding in combination with cyanosis the radiologic findings on the heart and the electrocardiographic pattern led us to suspect tetralogy of Fallot However the diastolic murmur with its maximal intensity within the apex and the superficial character which we have mentioned made us suspect that there was an abnormal coronary arteriovenous shunt The diagnosis of such a shunt was especially likely in the absence of clinical or other features indicative of pulmonary atrioventricular fistula rupture of an aneurysm of the sinus of Valsalva into the right cardiac chambers etc Hemodynamic and angiocardiographic studies confirmed this suspicion The conventional x ray film and electrocardiogram proved of little aid in the diagnosis of this type of coronary abnormality

The majority of authors agree that once this coronary abnormality is correctly diagnosed the patient should be operated upon Generally speaking the risk of operation should not be extreme Indeed in both of the patients who died postoperatively death could not be attributed to ligation of the abnormal vessel However in one patient [9] myocardial infarction supervened as a result of ligation of the coronary artery but it was successfully treated with the usual medical measures

On the contrary there is no agreement as to which is the best site for placement



Fig 4B The injection of the opaque substance was made with low pressure at the distal end of the surgical ligature of the coronary vessel Notice the branches arising at obtuse angles in the distal sense The right ventricle begins to fill with the opaque substance

of the ligature on the coronary vessel Some[11] postulate that the malformation should be occluded at the site of its abnormal connection and afterward ligated proximally to the origin of the aneurysm Others[9 15] have merely ligated the vessel once they are satisfied that no electrocardiographic disorders of any consequence appear with transient occlusion We believe that each patient should be considered individually and treated accordingly This depends upon the anatomy of the patient as visualized by the surgeon at the time of operation The minor anatomic details that canoot be visualized preoperatively will then become apparent The surgical technique will vary accordingly A careful analysis of the associated abnormalities should be made and the risk involved in their treatment carefully evaluated

Summary

We have described a case of multiple and complex malformations of the coronary arterial system i e single coronary artery which gave off several branches one of which connected abnormally with the right ventricular cavity so as to produce a shunt In addition there was severe pulmonary stenosis with a high right ventricular pressure This in turn maintained a right-to-left shunt through the abnormal coronary vessel Another similar shunt was present at the atrial level through an atrial septal defect

These malformations were suspected clinically Specialized studies (catheterization and angiocardiography) confirmed the diagnosis The patient was operated upon for ligation of the abnormal coronary vessel and correction of the pulmonary stenosis He died as a result of cardiac arrest

The hemodynamic pattern of this unusual case is discussed

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Clinical pathologic conference

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DR. LUCAS: This patient was first seen at the University of Minnesota Hospitals in 1959 at the age of 19 years. The case history reveals that he was born of a diabetic mother after a 7 month gestation. At the time of birth the patient had been considered to be normal, but development and the pattern of gain in weight were poor. A cardiac murmur was detected when he was 6 months old. The patient showed improvement in growth and development at about 1 year of age and, with the exception of occasional upper respiratory infections, he was thereafter symptom free until the age of 9 years. At that time dyspnea developed, becoming fairly severe during the next several months. Cardiomegaly was noted on roentgenographic examination. Upon the diagnosis of congestive cardiac failure, a digitalis preparation was administered.

Right-sided cardiac catheterization had been performed elsewhere when the patient was 10 years of age. The results of this procedure (Table I) were interpreted as indicating a large left-to-right shunt of about 6 liters per minute at the ventricular level. Pulmonary arterial pressures approached systemic pressures. The oxygen saturation of the femoral arterial blood was at the 92 per cent level, suggesting an additional right-to-left shunt. Simultaneous determination of pulmonary arterial blood oxygen saturation revealed a level of 87 per cent.

By the age of 12 years, the patient had improved significantly and the administration of digitalis was discontinued. He was essentially symptom free until the reappearance of dyspnea and easy fatigability at 17 years of age. During the next 2 years, until the patient was admitted to the University of Minnesota Hospitals at the age of 19, his condition remained essentially unchanged.

At this time the patient was a large, well-developed young man without cyanosis or clubbing. Examination of the heart revealed normal rate and rhythm, with no palpable thrill. A Grade 3 (on the basis of 1-6) harsh systolic murmur was heard along the left sternal border, maximally discernible at the third and fourth left intercostal spaces. The murmur was transmitted toward the apex. A soft diastolic murmur was heard at the second intercostal space and along the left sternal border. The second sound in the pulmonic area was markedly accentuated. On the basis of further studies to be presented, the patient was subjected to operation with the aid of extracorporeal circulation. The

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Table I Summary of data of both cardiac catheterizations

Age of patient (yr)	P (mm Hg) RA	RV	PT	FA	Blood oxygen saturation (per cent) IVC	SVC	RA	RV	PT	FA	Total pulmonary resistance (dynes sec cm⁻⁵)
10	1	90/0	94/ 9 64†	92/49 63†	67	57	63	86	87	92	570
19	3†	95 3	108/54 65†	130/75 93	—	60	66	91	90	96	200

*Catheterization performed elsewhere.
†Integrated mean pressure
RA Right atrium. RV Right ventricle. PT Pulmonary trunk. FA Femoral artery. IVC Inferior vena cava. SVC Superior vena cava.

patient died during the immediate post operative period

Dr Adams would you please discuss the diagnostic possibilities suggested by the material covering the patient's first 17 years

DR ADAMS The actual course of the disease in this patient represents one of several possible patterns in patients with ventricular septal defect In infants with severe manifestations including improper pattern of growth one may observe spontaneous improvement at about 1 year of age As symptoms in the infantile period may result from a large left to-right shunt so improvement may follow if the shunt becomes reduced possibly as a result of an increase in pulmonary vascular resistance With the exception of an episode of congestive heart failure at age 9 this patient did reasonably well until he was about 17 years old The dyspnea and fatigue appearing at that time may have resulted from organic pulmonary vascular changes that may complicate chronic pulmonary hypertension An increase in pulmonary vascular resistance would reduce the size of the left to-right shunt but at the same time a right to-left shunt might increase in magnitude or might appear An alternative explanation for the cardiac failure observed at 9 years of age is that an attack of pneumonia may have caused myocardial weakness through toxemia Pneumonia is a frequent complication of congenital cardiac disease associated with large left to-right shunts

Two phenomena are still puzzling to me One is the closeness of the levels of oxygen saturation in the pulmonary and in the femoral arteries This might suggest a common mixing chamber as seen at times in cases of single ventricle The other point is that cyanosis has not been mentioned in the clinical history Since the systemic arterial blood was desaturated when the patient was 10 years old I would suspect that cyanosis might have accompanied his symptoms if they arose from increasing pulmonary resistance Was the patient ever cyanotic?

DR LUCAS He was never noted to be cyanotic Dr Winchell you treated this patient on his admission to the University of Minnesota Hospitals Would you comment on your findings

DR WINCHELL The physical findings at age 19 have been reviewed and I need not repeat them The electrocardiogram (Fig 1) revealed normal sinus rhythm The P R interval was prolonged measuring 0 21 second The mean manifest electrical axis of the QRS complex was +60 degrees Precordial leads showed evidence both of right ventricular systolic overload and of left ventricular diastolic volume overload Dr Lester would you comment on the radiologic findings

DR LESTER Radiologic examination of the thorax (Fig 2) reveals marked cardiomegaly The main pulmonary arterial segment is very prominent and there is diffuse enlargement of the intrapulmonary arterial vessel The left atrium does not

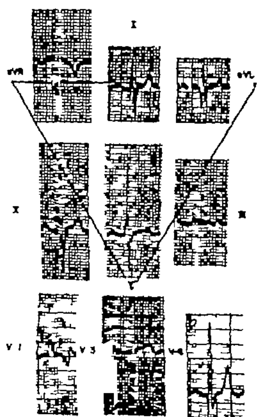


Fig 1 The electrocardiogram See text

appear to be enlarged The picture suggest a large left to right shunt with associated pulmonary hypertension

DR WINCHELL The working clinical diagnosis was ventricular septal defect with pulmonary hypertension A second cardiac catheterization was decided upon in order to establish more precisely the hemodynamic state

The results of the second catheterization suggested a massive left to right shunt at the ventricular level The pulmonary arterial pressure was unchanged from that observed on the first catheterization The oxygen saturation of the femoral arterial blood was 96 per cent and that of the pulmonary arterial blood was 90 per cent Inhalation studies with methyl I[131] were made with sampling of blood from the right ventricle right atrium and superior vena cava These indicated a left to right shunt at the ventricular level and no shunt at the levels either of the right atrium or of the superior vena cava Studies using Renografin I[131] and Cardiogreen were made by injecting each separately into the superior vena cava right atrium and right ventricle and recording in a femoral artery No right to left shunt was detected The calculated pulmonary resistance was observed to be in the normal range (200 dynes sec cm^{-5}) The next day a selective aortogram was made Dr Lester would you discuss these findings

DR LESTER The aortogram was made by injecting radiopaque material into the root of the aorta (Fig 3) No extracardiac shunt could be demonstrated On the basis of the aortogram we excluded corrected transposition aorticopulmonary communication and coarctation of the aorta

DR WINCHELL The foregoing findings led us to believe that this patient had a large ventricular septal defect with a large left to right shunt Aortography appeared to have ruled out other complicating lesions and the patient was considered to be a proper candidate for surgical correction of the ventricular septal defect Dr Lillehei would you describe the operative procedure

DR LILLEHEI After establishing extracorporeal circulation we opened the right ventricle This revealed a direct communication of the aorta with the right ventricle and a large ventricular septal defect It was apparent that closing this defect by



Fig 2 Posteroanterior roentgenogram of thorax

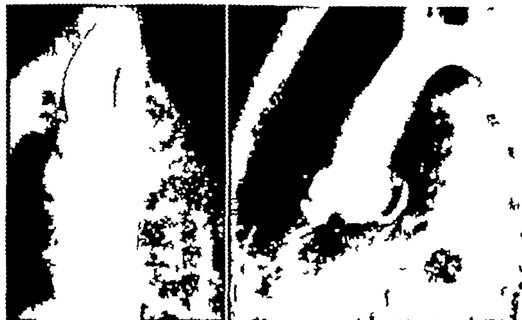


Fig 3 Selective aortogram *Left* Anteroposterior view Radiopaque material fills the ascending aorta and the coronary arteries The root of the aorta overlies the spine and is farther to the right than is anticipated in normal subjects The aortic valve appears to be at a higher body plane than normal *Right* Lateral view From the opacified ascending aorta it is apparent that the aortic origin lies more anterior than is normal See text for further discussion

directly opposing the edges would occlude the left ventricular outflow tract Therefore the corrective procedure involved placing a Teflon prosthesis in such a way as to divert the blood from the left ventricle into the aorta while excluding the two ventricles from intercommunication

DR LUCAS Dr Edwards would you please describe the pathologic findings

DR EDWARDS Necropsy revealed that the heart was grossly enlarged and globular in shape From the exterior the two great vessels appeared to be properly interrelated At the level of the base of the right ventricle however the aorta instead of curving downward to the left to take origin from the left ventricle communicated with the right ventricle at about the same body plane as did the normally placed pulmonary valve The aortic valve lay to the right of and only slightly posterior to the pulmonary valve The communication of the aorta with the right ventricle lay postero-inferior to the parietal band of the crista supraventricularis and in front of the tricuspid valve at about the junction of the septal and anterior leaflets (Figs 4 and 5)

A large ventricular septal defect was present which likewise lay postero inferior to the parietal band of the crista supraventricularis and extended down along the septal branch of the crista When viewed from the left ventricular aspect this defect was seen to lie in front of the junction of the anterior and septal leaflets of the mitral and tricuspid valves respectively Elsewhere its edges were composed of muscle The defect which measured about 3 cm in diameter represented the only outlet for the left ventricle No anatomic continuity existed between the left ventricle and the aorta It was possible to make an incision which gave the initial impression that the left ventricle and the aorta were in continuity Close inspection revealed however that the aortic and mitral valves failed to show the continuity which is normally present between these two structures They were in fact separated by a mass of muscle which represented the superior rim of the ventricular septal defect (Fig 5) Continuing with inspection of the specimen from this aspect it was apparent that (1) the left ventricle emptied through the ventricular septal defect into

the outflow part of the right ventricle and (2) that this part of the right ventricle in turn communicated with the aorta

Surgical correction of the abnormal communication had been accomplished by the placement of a Teflon prosthesis in such a way as to create a tunnel from the left ventricle through the ventricular septal defect into the right ventricle and then to the aorta The lower half of the Teflon septum had been sutured to the edges of the ventricular septal defect whereas the upper half of the prosthesis was sutured to the right ventricular wall along a line about 1 5 cm below the level of the attachment of the aorta to the right ventricle Placement of this prosthesis therefore created a tunnel through the ventricular septal defect into that portion of the outflow part of the right ventricle from which the aorta arose The subaortic part of the right ventricle was separated from the remaining portion of the right ventricle by the prosthesis (Fig 5) In this way blood entering the right ventricle was entirely diverted to the pulmonary trunk whereas blood entering the left ventricle was carried through the aforementioned channel into the aorta since the functional interventricular communication had been obliterated

The venous connections with the heart were normal The mitral valve appeared to be competent and the tricuspid and the pulmonary valves were essentially normal

The right ventricular wall was thick measuring up to 1 7 cm in thickness whereas the left ventricular wall measured about 1 5 cm in thickness The pulmonary trunk was wide having a diameter of about 3 cm The aortic diameter was about 2 cm Three aortic leaflets were present a right posterior a left anterior and a right ante





Fig 4 (For legend see opposite column)

Fig 4 Specimen of heart *Upper* Right ventricular view The interventricular communication (*D*) has been obliterated by the placement of the Teflon felt patch described in the text Above the ventricular septal defect lies the crista supraventricularis In more superior and anterior location lies the pulmonary valve (*P V*) The tricuspid valve (*T*) lies postero-inferior to the defect Communication between the aorta and the main part of the right ventricle has been obliterated by the prosthesis (*D*) There is no obstruction in the tract leading to the pulmonary valve *Lower* Left ventricular view and ascending aorta The prosthesis (*D*) not only obliterates the interventricular communication but also allows communication of the left ventricle with the upper portion of the right ventricle (*R V*) from which the aorta takes exclusive origin The apparent continuity between the left ventricle and the aorta is an illusion derived from the plane of dissection In the intact state the only outlet for the left ventricle was the ventricular septal defect whereas the aorta communicated directly with the right ventricle



Fig 5 Sagittal section through the entricles of the heart the aorta nd the region of the entricular septal defect The front of this specimen has been removed and the iew here shown is of the posterior portion of the specimen iewed from the front The plane of dissection was such that the pulmonary ah not shown since t lay i the nterior portion of the specimen along with the anterior wall of the aorta Between the arrow lies the prosthesis u ed to obl terat the interventricular communication At the same time this device allow communication of the left entricle (*L V*) with that portion of the outflow tract of the right entricle (*R V*) from which in t rn the ascending aorta (*A*) takes origin I contrast t the normal situation the anterior leaflet of the mitral val (*M V*) here separated from the ortic al e by a mass of mu cle (*M*) which represents the upper wall of the entricular septal defect *L S* Muscular portion of entricular septum

rior Arising above the right posterior aortic sinus the right coronary artery proceeded in the right atrioventricular sulcus without giving off any major branches to the anterior aspect of the heart The left coronary artery arose above the left anterior sinus and branched in an essentially normal manner giving off both anterior descending and circumflex branches

Histologic examination of the lungs revealed extensive alterations in the arterial bed (Fig 6) Large muscular arteries showed pronounced medial hypertrophy Some vessels of this category as well as some small muscular arteries showed intimal lesions Some were characterized by nonspecific fibrous thickening with or without focal hyalinization of the vessel wall whereas other intimal lesions showed formations of the characteristic plexiform lesion

Beyond zones of luminal narrowing by intimal lesions the media of the arterial wall was thin and the lumen widened at times excessively The arterioles and many small muscular arteries were thin walled and associated with wide lumina The picture of the vascular bed was that previously termed a high resistance-low reserve type or hypertensive pulmonary vascular disease Grade IV

Dr Neufeld you were involved in a clinical pathologic study of a group of cases in which both great vessels arose from the right ventricle as in this case Would you care to make some remarks about this subject

DR NEUFELD When both great vessels arise from the right ventricle pulmonary stenosis may or may not be associated I shall confine my remarks to cases which present without pulmonary stenosis since they are more pertinent to the case here discussed

We studied 8 cases of this malformation occurring without associated pulmonary stenosis[4] In each the clinical picture resembled that seen among some cases of large ventricular septal defect with pulmonary hypertension Clinically cyanosis and clubbing were very common A systolic thrill was usually present and was associated with a systolic murmur of the type present in ventricular septal defect The second pulmonic sound was accentuated in each case Electrocardiographic findings were of considerable interest In 7 of the 8 cases the mean manifest electrical axis of the QRS complex lay between −30 and −170 degrees and the instantaneous QRS vector in the frontal plan wed a counterclockwise loop with i above the zero line Roe examination revealed feature ent in ventricular septal c nary hypertension

From a hemodyn one could divide t studied into two g pulmonary vascula other with low p sistance In most of

he septal defect was large and therefore the pressures on the left and right sides were equal. Since volume of pulmonary flow depends on the relative levels of pulmonary and systemic resistance, with lower pulmonary resistance the pulmonary flow would be greater than the systemic flow. When pulmonary flow is extremely high and when good mixing occurs in the right ventricle, the level of oxygen saturation of pulmonary arterial blood may be nearly equal to the level of oxygen saturation of the highly oxygenated blood in the systemic arterial system.

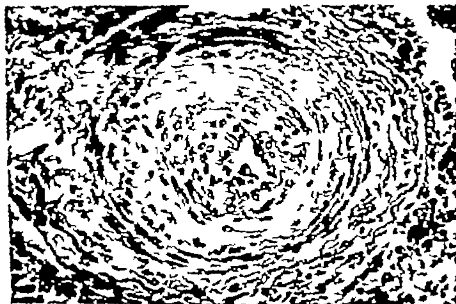




Fig. 6. Photomicrographs of pulmonary arterial vessels. Upper, A muscular pulmonary artery shows almost complete obliteration of the lumen by pronounced nonspecific concentric fibroblastic proliferation of the intima (hematoxylin and eosin, X 200). Lower, A pulmonary artery shows intimal thickening with fibrosis. Beyond, branch shows tortuosity and considerable dilatation with thinning of the wall. The pattern is commonly found in pulmonary hypertension together with pronounced increase in pulmonary vascular resistance (elastic tissue stain, X 100).

In the group of cases with high pulmonary flow the differential diagnosis as mentioned by Dr Adams includes single ventricle and origin of both great vessels from the right ventricle Determination of the anatomic positions of the semilunar valves and of the great vessels may help to differentiate these two conditions When both great vessels originate from the right ventricle the two great vessels are parallel in anteroposterior as well as in lateral views and the aortic and pulmonary valves are located at about the same body level

In the case presented here the electrocardiogram showed a mean axis of the QRS complex of +60 degrees in the presence of evidence for right ventricular systolic overload in the precordial leads The vectorial loop in the frontal plane was directed counterclockwise but a substantial portion of it lay below the zero line Thus the electrocardiogram suggests the usual type of ventricular septal defect

To the best of my knowledge no aortogram from a patient with this condition later proved at necropsy has yet been presented in the literature Dr Lester would you now in retrospect discuss the features of the aortogram

DR LESTER Review of the aortogram shows no evidence of an extracardiac shunt The ascending aorta lies to the right of the midline excluding the diagnosis of corrected transposition of the great vessels

Careful analysis of the films shows that the aortic sinuses (Valsalva) are slightly higher than is normal the aortic valve is at the projected level of the pulmonary valve In addition the ascending aorta is slightly *anterior* to its normal position particularly at the level of its origin The ascending aorta points in a vertical direction instead of pointing backward and to the left toward the left ventricle Furthermore in the frontal view the aortic sinuses are superimposed on the spine without the normal turn toward the left ventricle

Analysis of the position of the coronary arteries shows that the most proximal portion of the anterior descending branch of the left coronary artery takes a more horizontal course toward the left than is seen in the normal This appears to be due to the abnormally right sided position of the aortic origin as seen in the frontal view The most proximal portion of the circumflex branch of the left coronary artery is also displaced somewhat toward the right so that the proximal portion of this branch is superimposed on the left border of the dorsal spine

In retrospect the position of the aortic sinuses is abnormal This should strongly suggest the anomaly that was proved to be present

We have found that the diagnosis of origin of both great vessels from the right ventricle is best established by selective angiocardiography the injection is made into the right ventricle It may also be confirmed by left ventriculography in cases in which the aortographic findings arouse suspicion of this anomaly In the latter situation the catheter may be passed through the aortic valve into the left ventricle and an injection made in this area

DR WINCHELL Dr Lillehei since it seems possible to distinguish this malformation from the usual ventricular septal defect and from single ventricle would you discuss the importance of the differential diagnosis from the surgical point of view as well as the various surgical approaches and techniques used in treating this malformation

DR LILLEHEI Th success of the surgical treatment of almost any condition has a direct correlation with the accuracy of preoperative diagnosis Since diagnosis is never perfect an experienced and discerning surgeon often must and frequently can make successful allowance for varying pathologic lesions encountered unexpectedly at the time of operation

For this reason we have insisted for several years that every one of our patients who has a ventricular septal defect associated with severe pulmonary hypertension undergo preoperative selective aortography and often at the same time left ventriculography [4] This practice has been extremely rewarding in enabling us to identify preoperatively some of the serious conditions which may be associated with ventricular defect The forewarned surgeon is *thereby forearmed* and *the risk for the* patient is substantially lessened

In the case under discussion here as has been indicated the great vessels appeared from the exterior aspect to have a

normal interrelationship as is characteristic in this condition. Upon opening the right ventricle of this patient, however, we noted some important anatomic differences from the usual types of ventricular defects. Dr. Edwards has already commented on several of these differences. From the surgical standpoint, perhaps the most important of these was that although the defect in this patient was large, the ventricles were also very large. With the heart arrested (by selective hypothermia[4]) we could easily have approximated the edges of the defect, but to do so would clearly have occluded the outflow of blood from the left ventricle. Closure was therefore undertaken by placing a Teflon prosthesis in such a way as to obliterate the interventricular communication and to direct the blood from the left ventricle unimpeded into the aorta.

The pressures measured directly at the time of operation in this patient were of interest. These measurements confirmed the pulmonary hypertension noted when the cardiac catheterizations had been performed. The presence of residual pulmonary hypertension after the repair was considered to be indicative of high levels of pulmonary vascular resistance.

After the reparative procedure the heart took over well from the extracorporeal circulation. The patient was awake immediately after operation, and his appearance, blood pressure and cardiovascular status were excellent in the early postoperative period. About 24 hours postoperatively, faint icterus was noted, but since all vital signs were good, not much significance was attributed to this observation. During the next 6 to 8 hours, however, the jaundice deepened rapidly and the brachial blood pressure declined for the first time. The venous pressure and blood volume remained normal. Septicemia was suspected, but all blood cultures ultimately proved to be sterile.

The postmortem examination disclosed acute massive necrosis of the liver, but no discernible cause of this unusual complication was obvious. The most probable hypothesis appears to be that during the bypass procedure the somewhat soft plastic catheter in the inferior vena cava became kinked for a prolonged period while the attention of those at the operating table was directed toward repairing the cardiac defect.

DR. EDWARDS: Dr. Lucas' evidence relating to the pulmonary vascular bed is somewhat paradoxical. On the one hand, the data of the cardiac catheterizations indicate high values of pulmonary blood flow and normal or near normal pulmonary vascular resistance. On the other hand, the operative pressure studies and the histology of the pulmonary vascular bed point in an opposite direction. The persistence of significant pulmonary hypertension after closure of the interventricular communication and the type of pulmonary vascular disease suggest that the pulmonary vascular resistance was of high order.[3,5]

DR. LUCAS: In this case the values calculated for pulmonary blood flow and resistance were probably influenced by the physiologic artifacts that this condition imposes. The calculated values for pulmonary resistance depend, of course, on pulmonary flow rates as well as pulmonary arterial mean pressure. In the cardiac abnormality present in this patient, origin of both great vessels from the right ventricle, it is questionable whether assessment of pulmonary flow can be made from the oxygen values of blood in the pulmonary trunk. It is apparent from the anatomic arrangement that an obligatory shunt of all blood from the left ventricle to the right ventricle occurs. Some of the arterialized blood in the right ventricle, although arriving through the ventricular septal defect, is not "shunted" blood in the usual sense; this is because some of this blood is going to a normal goal, the aorta, albeit through an abnormal anatomic route. In fact, a common chamber exists, the right ventricle, which supplies both great vessels with mixed arteriovenous blood. Therefore, increased oxygen saturation in the pulmonary trunk does not necessarily reflect a high pulmonary flow, but may be an expression of mixing in the common chamber, the right ventricle. Therefore, the data of the cardiac catheterizations do not accurately reflect the true functional state in this patient.

Diagnosis: Origin of b[illegible] grea[illegible] from the right ventricle with [illegible] pulmo[illegible]

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Annotations

Tracers and lymph

Additions t our knowledge of the anatomy and functions of the lymphatics hav been slow in the 2 000 years since these essel wer first seen by members of the Alexandrian School about 300 B.C. and in the 340 year since the lacteals were described by Aselli in 1627 An annotation in *Lancet* April 1959 relates some of the studies of the lymphatic system from the time that William Hunter stated in 1784 that The lymphatics are the absorbing essel all over the body to the present-day studies with isotopic tracers F en the use of tracers is not new exemplified by the work of Mendel published in March 1896 tw months prior to Starling classic in the same olume

I his paper Mendel eported that the time from intra enous injection of sodium iodide to its ap pearance in the l mph of the thoracic duct of dogs as 4 minutes Since then other investigators using arious tracer sub tances ha studied the rates of uptake by and of flow in the lymphatic essel Hay nes cited that bromphenol blue traveled from ein to thoracic duct in 2 5 t 6 5 minutes and to skin lymphatics in 0 5 minute and that the rat of movement of ital red from ein to thoracic duct as from 2 to 8 minutes Iodinated albumin and dextran ha been timed from blood to thoracic duct in 7 to 10 minutes and horse serum injected subcutaneously in dogs has been detected in the l mph of the thoracic duct in 40 minutes and in blood in 3 5 hours Albumin injected into the hind pa of dogs has been reported to be in cervical lymph in 10 second and patent blue V injected into the hind paw of rabbits to appear in groin lymph in 20 to 30 second (2 to 3 second after absorption) I man E ans blue has been described on one occasion to require 20 to 30 minutes to ppear in the thoracic duct after intra enous injection Patent blue V 0 1 of 11 per cent aqueous solution injected intradermally in man formed streamers 15 cm long in 5 minutes but hen 0 05 of 1 per cent solution as used it as 20 minut before streamers 10 to 15 cm long ere sibl

The foregoing variations in the rates of movement from ein t the lymph of he thoracic duct or from skin to lymph may be reflection of differences in the quantity of substance injected and in the izes of tracer substances resulting in rious rates of escape from m nd rates of uptake by lym phatic essel None of these experiments permitted accurate timation of the rate of flow of fl d in given segment of extremital lymphatics The dif ference in pen-thoracic duct time nd ein-thoracic duct time however indicates that mor time is required for diffusion from the eins into the lym phatics than for flow from one point of the lymphatic system to another The rapid flow rates reported suggest that the olume of the lymphatic system is small For the flow time t be so short the olume per minut collected from the thoracic duct (about 1 c per minut in man or in dog) must represent l rge fraction of the total olume in the sy tem Determination of precise rates of flow within the lymphatic channel would be important n the evaluation of the role of the lymphatics in the transport of fluid from normal or edematou ex tremities and in the determination of the size of this compartment itself For mea urement of flow as distingui hed f om combined uptake and flow t is necessary t collect lymph containing tracer or to monitor for tracer at t sites along a l mphatic channel cephalad to the ite of injection and ab sorption of a substance taken up and transported only by the lymphatics Mo t of the smaller mole cules of dyes used to isualize lymph tics salts and radiopaque media are bsorbed by enous capillaries as ell or escape rapidly from the lymphat ics and therefore are not adequate Many sub stances of large molecular weight can serv but ell tagged lbumin is probabl the most practical tracer to utilize at this time The search for such tracer originated in 186 hen Von Reklinghausen demonstrated l mphatic ptake f egg oll 1 micron in diameter Since that time increa ingl larger particles ha been studied Am ng others Wegner in 1871 used rice starch particle that ere 8 micra diameter and Allan 1956 howed that paraffin asphalt pheres up to 22 5 micra in diameter entered the lymphatics Studies such as these t determine the limit of the size of particles taken up by the lymph t ha inferred that there is uni d ectional mo ement nd hat large part cles once ha ing entered do not escape from the l mphatics Thi is despread sumption ith egard t the ret rn of p ot ns t the circulating stem Result of infusi ns into the leg lymphatics of dog and reco ery f om the horacic duct suggest that particles ith molecular eight greater than 3 200 do not lea the l mphat once they ha entered[14] Barnes and Trueta provide further evidence that the l rger pr tein molecules are absorbed mainly or entirely by the l mphatics in their report that rabbit injected in the legs ith snake enom after all lymphatics had been severed survived wherea intact animals died This is supported clinically

the observ tion that edematous fluid from subjects with ob tructiv t pes of edema uscous nd yellow because of the concentration of protein whereas the edema fl id from subjects w th congestive heart failure relatively low in protein because this returned by the lymphatics in essentiall the same proportion as it is lost from the capillaries

Onl after precise mea urement of the rates of uptake of substances by and rates of flow within the l mphatics will it be possible to evaluate the importance of the exact size and olume of the enclosed lymphatic system The contents and size of this compartment mu t be con idered in any turnover or pace stud based upon concentration and content of the serum compartment especiall when diffusable tracers are used [14] It is conceiv ble because of the diffusability and free exchange of maller molecules that w th the exception of tran port of particles and large molecules this system may be considered to be a channel of flow in the nenclosed extracellular fluid or terstitial fluid pace It is also pos ible however that knowl edge of these rates may prov to be luable in studying procedures or drugs which ca influence rates of uptake and tra port of even the smaller molecules by the lymphatics thereby leading to better methods of therapy for all types of edema

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On the cause of S-T-segment shift of electrocardiogram in myocardial infarction

I tudying the causes of S-T segment hifts in myocardial infarction we used the phenomenon described by M G Udelnov in 1955 He showed that the application of necrotic tissue t the unaffected heart produces t the place of contact a relaxed zone of myocardium which does not tak part in the sy tole of the heart The ppearance of this zone called pre-necrotic lead to marked hift f the S-T segment of the electrocardiogram similar to shifts which are observed in myocardial infarction

For the elucidation of the cause of thi phenom enon it was necessary t nderstand the mechanism of the action of the necrotic tissue on the heart We supposed that it had ionic nature

I the first series of experiment made on frogs and rabbits the pieces f necrotic t sue were pplied t the heart in situ the pieces were enriched with pota sium sodium or calcium or conversely the pieces were applied aft preliminary extraction of these ions During the experiments found th t

the pplication of necrotic tis ue can only influence the myocardi m if the t ue contains potassium ion The presence or absence of calcium and sodium ions does not influence the bil ty of necrotic ti sue to cancel bioelectrical and contractile activity of myocardium which is in contact with it

On the ba is of these experiments the pre liminary conclusion reached was th t the action of necrot tis ue on the neighboring myocardium is connected with the tran fer of potas sium ion from necrotized tis ue t intact regions of myocardium in contact with it

This conclusion was checked in the second series of experiments in which necrotic tissue as applied to hearts in situ of rabbits and frogs and by means of the flame photometer quantitative determination of the content of potas ium and sodium was made in necrotic ti sue before and after its application t the myocardium in the myocardium in contact with the necrotic tis ue and in remote parts of the myocardium The experiments showed that in the case of necrotic tissue pplied on healthy myocardium pota sium ions are really tran ferred from necrotic tissue int the adjoining regions of the heart This lead t the appearance of electrocardiographic S-T-segment shifts of the type observed in cases of myocardial infarction

Therefore it was necessary to make clear whether there is such transfer of potas ium ions from the necrotic zone into contiguous parts of the myocardium under the conditions of the ppearance of necrotic area in the heart itself

W ligated the left anteri r descending coronary artery in rabbit nd t different times after placement of the ligature (from 5 minutes t 3 months) w determined the content of potassium sodium nd chloride in the zone of ischemia or necro nd in the conti uous regions nd—for comparison—in healthy part of the myocardium in the posterior wall of the left entricle. The data of the biochemical analysis were compared with electrocardiograms made before the rabbits were killed

W found that in the zone of necrosis potas sium content strongly decreases in comparison with the normal but that the content of sodium and chloride is significantly increased

I the regions of myocardi m contiguous with the necrotic region the amount of potassium increases in comparison w th normal Content of sodium and chloride decreases somewhat in comparison with that in healthy ti sue of the left entricular posterior wall

The increased amount of pota ium in tissues contiguous with the area of necro-i is observed for pproximately 25 day and coincides with significa t S-T segment shift and with the changes of the T of the electrocardiogram

The data obtained allow us to say that in the mechani m of formation of pre necrotic zone in the heart hich produces the S-T segment shifts of the electrocardiogram typical for myocardial infarction the exchange of pota ium ions pla the dom nating role

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Effective coronary perfusion pressure

The principal determinants of coronary blood flow are entral aortic perfusion pressure nd enous pressure in the right trium Central aortic pressure drives blood into the coronary arteries nd right atrial pressure resists their empt ing Pressure in the right atrium not only resists flow from the coronary sinus which drains m st of the blood deliv ered by the left coronary artery but lso flow from the anterior cardiac eins hich drain most of the ri ht entricula coronary flow Thebesian enous d ain age int the right atrium represent ery small amount of the total coronary enous return but this too resisted by right trial pressure

Perhaps because the right trial pres ure is normally so low (3 or 4 mm Hg mean) the significance of it res tance t coronary flow is so me times forgotten I studies on hemod namic changes associated w th experimental pericardial tamponade Bisson Morga Walch and Sarnoff recently dem on trated the practical importance of considering b th of the tw principal determ nant of coronary flow I experimental shock their dog ith cardiac tamponade d ed hen mean aortic pres ure fell t 50 mm Hg hereas control dogs without tamponade survived mea aortic pressures of 25 mm Hg The difference in surv l was attributed to the ele ted right trial pres ure dogs ith cardiac t mponade The usef l term of effectiv coronary perfusion pres re as introduced to express the diff ence between central aortic pressure and right trial pressure FCPI = Ao − RA This simple concept ha not received the clinical attention deserves

I addition t pericardial tamponade classic example of cond tion in hich central aortic pressure and cardiac output re falling t the same time that right trial pre re is ri ing there are a number of analogous clinical conditions I congestiv heart failure entricular end-diastolic pres ure becomes ele ted forcing an incre in trial pre sure A right trial pre sure rises due t congestiv heart failure an condition previously associated ith reduced cent al aortic pressure the same reduction in effectiv coronary perfusion pres ure occurs in pericardial tamponade Thi is seen in aortic tenosis in hich the central aortic pres ure t fixed

level or during acut myocardial nfarction which reduced central aortic pressure is commou problem early the clinical course I either of these condition ele tion of right trial pres ure is quickly expressed as reduced effectiv coronary perfusion pres ure. *supporting the gra ty of the ppear ce of ongestiv failure in these conditions*

Red ced effectiv coronary perfusion pressure due t ombination of right trial hypertension plu aortic hypoten ion not only renders the entire my ocardium more anoxic than does simple reduc tion of ce tral ortic pressure alone but in an rea of m ocardium pre iously ischemic due to focal coronary scleros s this degree of f rther depres tion of oxygen may make the critical differenc between surv val or nfarction

An excellent example of udden reduction effectiv *coronary perf sion pre re is een in* acut pulmonary embol m The increase in pulmonary ascular resi tance much of which is reflex in origin cts in two directions It not only abruptly elev *tes the right entricular nd right trial pres* ures the latter elev tion being compounded if the tricuspid h becomes incompetent but it also bruptly reduces the olume of blood tra ersing the pulmonary ascular bed t fill the left heart thereby reducing cardiac output nd central aortic pressure Although there may be some reflex effect on coronary artery tone in cut pulmonary em bolism the commonly observed acut myocardial anoxia must be related more t the sudden re duction in coronary perfusion

Chronic pulmonary hyperten of any etiology can produce a similar effect on coronary perfusion nd the refractoriness of conge tiv failure in the case of or pulmonale may be due partially t this f ctor Pulmonary hyperten ion and the resi tance to normal blood flow into the left heart may be either at the level of the pulmonary arterioles or stenotic mitral al or both I all diseases with pulmonary hyperten ion the development of competence of the tricu pid alv is a critical event beca se it further levates right trial pres re and *reduces effectiv e coronary perf ion pre sure* Che t pain which occurs cases of pulmonary hyperten ion of any etiology ma ell be due to myocardial ischemia so induced pouint prev iou ly suggested by Dresdale Schult nd Michtom

It is likely that an acut r e in pulmonary rterial pressure (as in acut pulmonary embolism) is les w ll tolerated by patients w th chronic pulmonary hypertension tha b patients w th previou l normal pulmonary arterial pres res because of the ociated right entricula hypertroph in the former A *thick right entricle which has alread* been generating pres re that pproaches that in th central aorta lea es the patient les range of safet in regard t effectiv coronary perfusion pressure especially if the right entricle has been f iling nd the end-dia tol pres ure elev ted or if the tricu pi l al is incompetent A patient w th long standing mitral stenosi hronic pulmonary h perten on a l hypertrophied right en tricle tolerates poorl ny add tional increase in pulmonary arterial pres ure nd one of the im portant reasons is the effect on coronary perfusion Whether a *r ght entricle of normal thickness* dilates more easily during acute pulmonary hyper tension and more often produces tricuspid al ular incompetence is conjectural as is the possibly dif ferent effect that this might ha on effect coronary perfusion pressure

A y dise which restricts normal entricular filling and consequently raises trial pressure doubl reduces effecti c coronary perf ion pressure be ca e of combined right trial hypertension and aortic hypotension This pplies not only to peri cardial tamponade but also to constrictiv peri card ti subendocardial fibroelastosi primary cardia amyloidosi and severe myocardial fibrosi (due to long standing coronary sclero or se ere inflammation and repair or hemachromatosi)

Gregg[1] ha lucidl d cu sed the ma y complex factors which contribut to coronary blood flow *and has emphasized that the left entricle furnishes* not onl the pressure head responsible for coronary artery filling but also the major resistance to coronary filling during systole Furthermore the rate *and olume of flow in the proximal coronary arteries* the distal coronary arteries and the coronary eins are by no means parallel Thus phasic ariation an elev ted right trial pressure may prod ce different effect on coronary empty ng if th elev tion is mainly in the wav (as in tricuspid stenosis) or in the v w e (as in tricuspid regurgitation) whether one has more deleterious effect than the other on coronary empty ng has received little ttention

Therapeutically t is important t consider the *roles of both right trial pre sure nd central aortic* pre sure states associated w th reduced coronary flow Phlebotomy for the enous hypertension of constrictiv pericarditis may ha catastrophic results for lthough t eff ctively reduces enou pressure it simultaneou l reduce blood ol me cardiac output and central aortic pressure thus the salutary effect t the enous end of coronary flow may be neutralized nd even overbalanced by the los of perfusion pressure t the aortic end The reverse as clearly how in the studies of Binion nd his colleagues hen they produced improv ment in coronary flow in pericardial tamponade by the administration of systemic sopressor agent (metaraminol)

Clinical cond tions manifested by both right trial hypertension and reduced central aortic pres sure hould ha e tial therapy directed t restora tion nd maintenance of central aortic pres ure Thi alone may ufficiently improve coronary flow so that myocardial efficiency returns nd enous hyperten ion is reduced I certain circumstance uch congestive failure during acut myocardial infarct on t may be necessary to employ both adm nistration of sopressor agent and phlebot omy in uch cases con ideration of their influences on effectiv coronary perf ion pres re certainly indicates that effort to elev t central aortic pres sure should precede effort to reduce right trial pressure by phlebotomy

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The Sturge-Weber syndrome

The literature abounds with reports of cases in which there are coexistent congenital vascular anomalies of the skin and of the central nervous system. The Sturge Weber malady is the most frequently encountered of these albeit a rare enough condition in individual clinical practice. A motley group of cases has been described under the title of Sturge Weber disease and Alexander and Norman in a recent concise monograph put forward a plea for a more rigid definition of the disease conforming to the original descriptions. It is insisted that the presence of a facial naevus and of angiomatosis at the leptomeningeal level are prerequisites for the diagnosis. If these criteria are accepted a remarkably uniform clinical picture emerges. The angiomatosis on the surface of the brain is usually revealed by extensive deposits of cortical calcification which as these authors show from the literature and in one of their cases are rarely detectable radiologically before the age of about 2 years. The calcifications have a characteristic gyriform pattern which however is not exclusively confined to the Sturge Weber condition.

Several important deductions have been put forward. It is noted that the naevus affects the supraocular part of the face in true Sturge Weber disease and an embryologic correlation is offered in explanation of this feature.

The histories indicate the frequency of a promising start in life and even of intellectual precocity shattered by the advent of epilepsy. Lobectomy which has been practised since 1936 (Olivecrona) should be considered in infancy before epilepsy has occurred if the facial naevus has the requisite distribution and if small local exploration of the occipital or parietal regions of the brain reveals the typical meningeal vascular anomaly. In this manner experience may reveal how far the epilepsy contributes to the serious intellectual retardation which is also the rule in those cases.

Operation revealed conspicuous cyanosis of the abnormal meningeal vessels in several cases. It is interesting that there may be a parallel between the cardiac instability which results from the territorial anoxia of coronary occlusion and the cerebral instability which is manifest as epilepsy in Sturge Weber disease.

Evidently in the more gross examples with dense cortical calcification the electrical activity shown in direct recordings from the exposed cortex is minimal yet it is grossly dysrhythmic in the adjacent cortex of normal appearance. Removal of this electrically silent area may have a remarkable steadying effect on the tracing from the rest of the cerebrum with substantial clinical benefit in sequence. The electrical silence may be due to retention of carbon dioxide in the calcified cortex underlying the abnormal vessels and has an effect on the electroencephalogram similar to that observed when a main bronchus is clamped at operation (Wilson[3]).

Falconer and Rushworth have recently described their encouraging experience with hemispherectomy in patients with Sturge Weber syndrome who already had hemiparesis.

The recent suggestion by Hayward and Bower[5] that the chromosomal abnormality which they found in one case of Sturge Weber disease may be characteristic has not been confirmed in an investigation of Alexander and Norman's cases nor by Lehmann and Forssman. Swedish recorded examples of the true Sturge Weber anomaly are found to occur in a family tree nor was there any association with congenital heart disease.

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Letter to the Editor

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To the Editor

We are writing on behalf of the University of Hue the free Republic of Vietnam The University which opened its doors in 1957 has in the three and a half years since that time nearly doubled its enrollment thereby justifying the faith of its founders that this new institution would fulfill a vital need in this crucial part of the free world

Last fall the University expanded its activities by opening a school of medicine—the world newest—to provide a full seven year program of medical education in all fields neurology microbiology nursing public health tropical medicine etc

As part of our program of assistance to the people and institutions of Vietnam we have undertaken to obtain for the medical school certain books professional journals and other resource materials based on needs submitted to us by the medical staff of the Hue city hospital (which is being used by the University for its training program) Among the publications which the University has requested is the *American Heart Journal* We would very much appreciate your bringing this fact to the attention of your readers who may wish to dispose of back copies of the Journal in a worth while manner Such a gift would be an invaluable addition to the University limited resources and would be further evidence of the community of feeling which exists among educators and publisher throughout the free world

All donations may be sent to this office where each will be catalogued and prepared for shipment to Vietnam We should like to point out that gifts to the American Friends of Vietnam—including gifts of this nature—are deductible from taxable income each donor will receive a formal receipt acknowledging the value of the contribution

If there is any further information you would like either about the University of Hue or about our own organization please do not hesitate to get in touch with us

Louis Andreatta
Executive Secretary
American Friends of Vietnam

Book reviews

MODERN TRENDS IN CARDIAC SURGERY. Edited by H R S Harley M S F R C S Consultant Thoracic Surgeon United Cardiff Hospital and Welsh Regional Hospital Board New York 1960 Paul B Hoeber Inc 782 pages Price $1

This book by t enty tw Briti h surgeons an interesting expression of curr t Brit h surgical practice in cardiac urgery This book makes no attempt to exhaustively cover the entire field of cardiac surgery but nonetheless tremendou amount of information is available in it 28 pages Th book as edited by H R S Harley a Welsh thoracic urgeon and the tw ch pters hich he contributed on hemodynamic altera tions in cardiac disease and on rgical treatment of mitral stenosis are especiall informat All of the chapters in this book are ery easy t read With ju t a little expansion this book could ery ea ily be the out tanding text n the field of cardiac urgery

A few definite deficiencies that exi t are related primarily to the nature of the subject material itself and the rapid alteration that are taking place in this field t all times For example in the chapter on cardiac arrest there no reference to the method of closed chest ma sage described by Kouwenhoven and certain to achieve ide pread use This not an over ight I am sure but simply due t the fact that the book ent to the printer before this information became available.

HEART SOUNDS AND MURMURS A CLINICAL ND PHONOCARDIOGRAPHIC STUDY By P A Ongley Consultant in Pediatrics Mayo Clinic Rochester Minn H B Sprague Board of Consultation Massachusetts General Hospital and Past President American Heart Association M B Rappaport Former Head of Department of Electrophysiologic Research Sanborn Company Waltham Mass A S Nadas Cardiologist Children Hospital Boston Mass New York 1960 Grune & Stratton Inc 300 pages Price $9 5

This book di ided int ix sections I H tory and Physics II Heart Sounds and Murmurs III Diseases of the Heart Valves IV Rheumatic Heart Disease V Congenital Heart Disease VI Miscellaneous As the titles imply there some repetition of content the arious sections

Approximately the first one hundred pages of this small olume are de oted to the physic of sound and historical pects as hey relate t the development and application of auscultation and phonocardiograph As might be expected much of this is based on previou ly published ork of Rappaport and Sprague The method of phonocardiography which form the basis of the book are those advocated by these t o investigators in particular the logarithmic ad stethoscopic method used in recording the heart sound from the chest all Inadequate coverage is given to techniques nd method ad ocated by other authors and publi hed nder such names as calibrated phonocardiograph fil tered phonocardiography selectiv phonocardiography spectral phonocardiography and intracardiac esophageal and tracheal phonocardiography This lack of comprehensiveness the coverage of methodology is not necessarily defect however provided that the reader somewhat familiar with the over all phonocardiographic literature

The other pproximatel tw hundred and fifty pages of the book deal more pecificall with the more clinical pects of auscultation and phonocardiography These sections excellentl serv to tran fer the recently accumulated wealth of research information dealing th cardiovascular sound into the realm of clinical pplication Very few seful features in clinical auscultation ha e been omitted Coverage incomplet however in certain area namel pericardial friction rubs extracardiac sound and a few of the finer pects of auscultation in congenital heart disease

I general thi book recommended for those interested in auscultation and phonocardiog raph The present tion i fairly well organized The paper and printing are excellent the illu tra tions are good and the indexing sat factory

CLINICAL DISTURBANCES OF RENAL FUNCTION By Abraham G White M D F A C P Associat Vi ting Physician nd Chief of the Renal Disease Clinic Queens Hospital Center J maic N Y Philadelphia and London 1961 W B Saunders Company 468 pages Price $10 50

This book meant for the practicing ph sician facing cl nical problems in hich there is disturbance of kidney funct on There are xteen hapters th such titles as Acute Renal F il ure Obstetric Aspects of Renal F nction nd Surgical Aspects of Renal F nction Each subject discu sed from the point of iew of pathogenesis relationship of clinical features to disturbed function nd the logical therapy The discuss on ery readable and all times the thor t pains to oid being dogmatic The reasons underl ing the methods of therapy are given nd the idence ailable to support the reasons is indicated I order to keep the text simple references onl to major orks or reviews are given nd the bibl ography is short I gener l the opin ons expressed conform to the prev iling op nion of modern renal workers For all of this the book cannot but be praised More que ionable is the selection of subject that ha been included in this book Sections on the var ous endocrine diseases hepatic cirrhosis nd the principles of genetics hardly seem necessary

Inev tably some criticism ca be made of individual parts of the book such as the omission of mention of the use of anabolic steroids in the management of acute renal failure although t

care for them in patients with disturbances of pregnancy strong and whereas the importance of *differentiating dehydration figures from acute* tubular necrosis is repeatedly stressed no real help is given on how to do it (such as urine urea concentrations or urine specific gravities) Another fault is the system of cross references giving chapter numbers only which is poor one

The book is good one and addition to the practicing physician to whom it is directed should provide helpful reading to medical students and others who are interested in renal problems

Announcements

A Course in Interpretation of Complex Arrhythmias will be given at Michael Reese Hospital by Louis N Katz M D Richard Langendorf M D and Alfred Pick M D This is an *advanced* course intended only for experienced electrocardiographers The *class will meet daily* from 9:00 A M to 5:00 P M Dec 4 8 1961

Further information and copy of the lecture schedule may be obtained from Miss Beverley Petzold Secretary Cardiovascular Department Medical Research Institute Michael Reese Hospital and Medical Center Chicago 16 Ill

The Joint Annual and Scientific Meetings of the Canadian Heart Association and the National Heart Foundation of Canada will be held in Vancouver B C Nov 13 18 1961

Address enquiries to Dr John B Armstrong National Heart Foundation of Canada 501 Yonge St Toronto 5 Canada

Final plans have been announced for the Eleventh Annual Instrument Symposium and Research Equipment Exhibit to be held Oct 9 12 and Oct 10 13 1961 respectively at the National Institutes of Health Bethesda Md

Under the auspices of the local sections of six national professional societies more than 20 scientists actively engaged in research in their specialties will report on recent developments in research methods and instrumentation

At the research equipment exhibit 121 of the nation leading manufacturers of electronic mechanical and optical instruments for laboratory and clinical research will display a wide array of the latest scientific apparatus

This year symposium will consist of seven sessions Dr Alton Meister Chairman of the Department of Biochemistry Tufts University School of Medicine will preside over the opening session dealing with applied gas chromatography Other topics on the 4-day scientific program are factors influencing the interpretation of infrared spectra optical rotatory dispersion thermogravimetric analysis electron probe analysis the application of physiologic instrumentation to clinical problems and electron magnetic resonance Chairmen of the discussion sessions include Dr Ellis R Lippincott University of Maryland Dr Ulrich Weiss National Institute of Arthritis and Metabolic Diseases Dr Saul Gordon Fairleigh Dickinson University Dr Isidore Adler U S Geological Survey Gerald S Cohen Division of Research Services N I H *and Dr Edwin D Becker National Institute of* Arthritis and Metabolic Diseases

Dr James A Shannon Director of N I H will welcome symposium participants at the opening meeting October 9 at 8:00 P M Scientific sessions will continue through the week with two meetings daily at 2:00 P M and 8:00 P M The closing session will be held October 12 at 2:00 P M

The research equipment exhibit will be open daily from 11:00 A M to 5:00 P M October 10 13 On October 11 the exhibit will remain open until 9:00 P M

Six of the exhibiting firms will hold special in*strumentation clinics to demonstrate the research* applicability of their newest equipment Instruments shown will include a electronic spectrophotometer refrigerated cell fractionator atomic absorption analyzer immunoelectrophoresis accessories electronic hematocrit and a protein monitor Demonstrations will be given October 11 12 and 13 from 9:30 to 10:15 A M and 10:1 to 11:00 A M

For additional information write or call James B Davis National Institutes of Health Public Health Service Bethesda 14 Md Phone OLiver 6-4000 Ext 2315

The American Urological Association offers an Annual Award of $1 000 (first prize of $500 second prize of $300 and third prize of $200) for essays on the result of some clinical or laboratory research in urology Competition is limited to urologists who have been graduated not more than ten years and to hospital terns and residents doing clinical or laboratory research work in urology Animal research is not necessary

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association to be held at the Bellevue Stratford Hotel Philadelphia I May 14 17 196

For full particulars write to the Executive Secretary William P Didusch 1120 North Charles St Baltimore 1 Md Essays must be in his hand before Nov 15 1961

American Heart Journal

October 1961 Volume 62 Number 4

Editorial

Ageing and radiation

G. J. Neary, Ph.D.
Harwell, England

The starting point of my own reflections on the general problem of ageing is the commonly held view that whole body irradiation of an animal can in certain circumstances speed up natural ageing. This generalization has only been checked experimentally to a limited degree. Certainly irradiated animals normally have a reduced survival time and after a single dose of irradiation or after lifetime low level chronic irradiation the pathology at death is broadly the same as in unirradiated control animals. But even using only terminal data of this sort for CBA mice it is possible to argue that there is an intrinsic process of ageing enhanced by radiation which operates from the start of life and is virtually complete by the time the changes of old age begin to appear; until then the process has little outward physiologic manifestation or effect on survival fitness. The argument is quite simple but first it is necessary to clear a little ground and establish a common conceptual currency.

Two basic questions may be posed: Why does an animal die? Why is there a variation in the age at death of comparable individual animals. One type of answer emphasizes the element of randomness in mortality and the individuals in a population are often tacitly assumed to be identical. The age specific death rate, the so-called force of mortality, is often interpreted as the probability that any survivor will die in a unit interval of time at that age. The observed progressive increase of the force of mortality after a certain age is attributed to a progressive decline in the physiologic state or vitality of the population and the individuals thereof. The logarithm of the mortality rate, the Gompertz function, increases approximately linearly with age and so it has been an attractive idea to regard this quantity as an intrinsic index of physiologic age.

A quite different type of answer to the two basic questions concentrates attention on the individual: his life span in any given environment is predetermined by his initial genetic endowment. Merely to recognize the existence of this theoretical possibility is of considerable importance because it then has to be admitted that the progressive increase with age in the age specific death rate may result merely from the form of the distribution of individual life spans in the population. The concept of a force of mortality would then be out of place and there need be no relation between the Gompertz function and the physiologic state either of individuals or of the surviving population as a whole. In most quantitative deterministic theories ageing is regarded as some process of change within cells, probably in their genetic apparatus. It is clear, however, that the fate of the individual cannot be considered solely in terms of the fate of a component cell. Even though changes within cells may be the root cause of ageing, it would be in

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sufficient to consider only the primary process without reference to the whole sequence of events in the complex of interacting physiologic systems

In practice both random and determinististic factors undoubtedly play some part For the human white female population of the United States at present the difference in age at death of identical twins is much less than the standard deviation over the whole population On the other hand there has been a significant reduction in mortality during the past hundred or so years in most economically developed countries The reduction is chiefly in the acute causes of death and has been most marked in early and middle life the chronic degenerative causes have shown a much smaller change Hardin B Jones has argued from such facts that there is a causal relation between disease experience and subsequent susceptibility to disease but so far animal experiments have provided no definite confirmation of this theory

My own view is that even if all adverse external influences could be removed an intrinsic process of ageing would remain which is fundamental inevitable and irreversible The process proceeds in two successive stages induction and development which together occupy the whole lifetime During induction changes occur within individual cells these naturally occurring changes can also be produced by radiation Because of homeostatic regulation the production of the changed cells which may or may not be viable produces little physiologic impairment until a certain level of inductive change has been reached Then homeostasis breaks down rather rapidly and the second stage development sets in It involves a different level of organization and consists in physiologic interactions which proceed autonomously and autocatalytically entailing rapid physiologic impairment culminating in death development thus corresponds to senescence Once it has been triggered further inductive change is superfluous so that further irradiation at this stage is ineffective provided that it is not sufficiently intense to have direct physiologic effects The primary process of induction is genetically determinate and little influenced by random factors the second process of development may because of its greater complexity be subject to such factors

One of the essential features which distinguishes this picture of ageing is the approximate constancy of physiologic competence for survival during induction which in mice occupies about 80 per cent of the lifetime physiologic ageing is mainly a phenomenon of senescence The opposite assumption which has usually been made that all of the injury produced by the simple passage of time or by whole body irradiation is necessarily expressed as proportional physiologic injury has in my opinion hindered the understanding of the problem especially the analysis into reparable and irreparable injury As Shock has pointed out some indices of physiologic capacity are more or less constant throughout life others appear to show a decline but such data are usually obtained from different groups of individuals at different ages What we do not know of course is what happens to a single individual as he progresses through his life cycle The range of variation between individuals of the same age is almost large enough to admit the possibility that there is little change in the individual before senescence In any case some of these indices refer to maximum physiologic capacity which may have relevance only to survival from the more extreme accidents in the presenescent period The important question is whether there is a marked increase in the rate of loss of physiologic capacity during senescence

The experimental data which suggested to me the foregoing scheme were obtained in survival studies of chronically irradiated CBA mice under carefully kept conditions so that external disturbing factors were minimized It is generally found that the mean life shortening of a group of mice or rats is roughly proportional to the mean accumulated radiation dose It is reasonable to expect therefore that the life shortening for one individual will be roughly proportional to his individual accumulated dose If exposed to a given dose rate throughout life the naturally longer lived animals would receive a larger accumulated dose and their absolute life shortening would exceed the average but the proportional life shortening would be

the same for all The cumulative mortality curve against time for an irradiated group would thus correspond to that of a control group but with the time axis contracted The standard deviation of survival time would be decreased by radiation in the same proportion as the mean survival time itself Conversely the slope of the Gompertz plot would be increased In fact however these features were not found with CBA mice Up to about 15 rems per day there was no reduction in dispersion of survival times even though the mean survival time was nearly halved the cumulative mortality curves were merely displaced from each other not contracted the Gompertz plots were roughly of equal slope These results would be explicable if the induction time and radiosensitivity were nearly the same for every member of a group of these genetically homogeneous mice The effective accumulated dose during induction and the shortening of induction time relative to controls would then be the same for all The duration of development was unaffected by radiation and was statistically the same for irradiated and control animals a value of about 180 days was deduced The Gompertz plots were very steep and roughly linear during the period of development before that in the induction period the slope was much less Further analytical details may be found in the original paper

An understanding of the basic process of cellular change during induction would not only be of great theoretical interest but also of practical importance in providing perhaps a basis for extrapolation of life shortening data on animals to man So far however little sure evidence is available from the radiobiologic data The dose response is linear which is clearly consistent with a cumulative injury due to irreversible changes in cells The linearity argues against the primary process being one of chromosome structural damage and would suggest rather somatic gene mutation The fact that short single doses of X or gamma radiation are some three times as efficient as the same doses delivered chronically at low rates indicates a dose rate factor which is not expected for gene mutation Moreover the large size of the doubling dose (some thousands of rems) is surprising for a gene mutation unless cell selection for the radiation mutants is much more severe than for the natural mutants Perhaps the site of the change is not in the chromosomes at all in some organisms ageing seems to be a cytoplasmic phenomenon

It is not known whether the cell change responsible for ageing causes the death of irreplaceable cells or reduces the competence of cells for certain functions or whether it results in autoimmune reactions between changed and normal cells or between changed cells themselves It is also not known whether all the cells of the body are subject to the particular form of change or whether only special systems of cells are important—these latter might constitute the homeostatic systems supposed necessary to keep spontaneous autoimmunity suppressed The question obviously arises as to whether the primary process is the same in different organisms even as closely similar say as mice and men If this assumption is made for the latter particular pair we may note that according to the simplest theory the life shortening per rem is numerically equal to the ratio of the rate of cell change produced by unit dose rate to the spontaneous rate There is no obvious reason why this ratio should be very different for a mouse and a man and so the life shortening per rem in man may be only 0 08 days the figure found for mice It has frequently been assumed that the life shortening per rem in man would be greater than in a mouse in the ratio of the natural life spans but the logic of this is not apparent It is also interesting to speculate how the development period of 6 months in the mouse would be extrapolated to man I leave it to physicians to decide whether a figure of 6 months or some 25 times this i e about 12 years is a better estimate of the period of senescence in man

REFERENCES

1 Jones H B A special consideration of the ageing process disease and life expectancy Advances Biol Med Phys 4 281 1956
2 Neary G J Ageing and radiation Nature 187 10 1960
3 Shock N W Age changes in some physiological processes Geriatrics 12 40 1957

Clinical communications

A clinical study of shock occurring during acute myocardial infarction An analysis of 58 cases

Howard E Heyer M D
Dallas Tex

Severe shock has been estimated variously to occur in from 7 to 20 per cent of the patients suffering from acute myocardial infarction Its development is a grave complication and is associated with a high mortality rate The importance of early recognition of this syndrome has been emphasized since prompt therapy appears to increase the chance for survival The time at which shock occurs after the development of an acute myocardial infarction and the natural life history of this *condition is therefore of great importance* in its recognition and management

It is the purpose of the present paper to report a clinical study of 58 cases of this syndrome Adequate data were available to permit a detailed study of cardiogenic shock of its frequency of occurrence clinical characteristics mortality and various features affecting the prognosis

Clinical material methods, and criteria

Seven hundred and fourteen cases of acute myocardial infarction were surveyed in the present study There were 546 men and 168 women 161 patients succumbed a *mortality rate of 22 5 per cent* The diagnosis of acute myocardial infarction was made on the basis of a typical clinical history plus characteristic electrocardiographic findings Additional confirmation was obtained by autopsy in 14 of the 29 patients who succumbed after myocardial infarction

The age distribution ranged from the fifth through the ninth decade (Table I) The greatest number of cases occurred in the sixth decade The ages varied from 43 to 83 years Seventeen patients in the group with shock were hypertensive or were known to have been hypertensive prior to the onset of shock in many others *preceding hypertension was suspected but* not proved

Frequent determinations of the blood pressure were made during the first week of the hospital stay In many patients during the first 48 to 72 hours these readings were made at intervals of 1 hour both day and night The criteria for the diagnosis of shock in patients who were suffering from acute myocardial infarction included the following (1) Definite clinical signs of shock were present these included sweating weakness pallor or cyanosis absent or small volume pulse moderate tachycardia nausea and often a dulled sensorium (2) The level of blood pressure fell to 80 mm systolic or below in patients previously hypertensive readings below 90 mm systolic were considered as shock levels

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Table I Myocardial infarction with shock Age distribution and mortality by decades

Age group (yr)	Number of patients	No. of deaths	Mortality (%)
30–39	0		
40–49	5 (9%)	1	20
50–59	25 (43%)	9	36
60–69	13 (22%)	8	62
70–79	13 (22%)	11	85
80–89	2 (3%)	0	—

[illegible] all fatal cases death was attributable directly to the effects of cardiogenic shock

Hypotension alone was not considered prima facie evidence of shock since as will be seen some patients exhibited hypotension without other confirmatory signs of the shock state In addition patients in whom the fall in blood pressure could be attributed to some other primary initiating cause such as hemorrhage pulmonary embolism severe tachycardia acute cerebrovascular accident or marked cardiac failure were not included in the present series Fifty eight patients with shock after acute myocardial infarction met these criteria and are the subject of the present study Patients who lived for 10 days after therapy for shock was discontinued were classified as survivors

Results

Mortality Fifty-eight patients (8 per cent) of the group of 714 with acute myocardial infarction developed shock The total mortality in this group with shock was 50 per cent Two of these 58 patients succumbed before treatment was begun and 2 received inadequate therapy (with l norepinephrine being administered for less than 1 hour prior to death) In the other 54 patients who received adequate therapy the mortality was found to be 46 per cent (Table II) This mortality is comparable to that found in other adequately treated groups and is slightly more favorable than that reported in some series It is also a marked improvement over the survival rate to be expected in patients treated by nonspecific means without vasopressor substances in whom the mortality has been reported to range from 70 to as high as 93 per cent

Time of onset of shock In the great majority of instances the time of onset of the myocardial infarction could be established with reasonable certainty In 62 per cent of the patients shock followed the onset of myocardial infarction within 24 hours (Fig 1) Within 72 hours the vast majority of cases of shock had developed 91 per cent of the cases had appeared by this time

As has been reported previously a few cases may be delayed until later in the course of the illness One case occurred on the fourth one on the fifth two on the sixth and one on the eleventh day after the onset of acute myocardial infarction If the majority of cases of shock are to be detected promptly therefore patients with acute myocardial infarction must be observed most closely in the initial period of 72 hours

Clinical features and classification

Hypotension without shock In a review of this series of 714 patients hypotension without clinical signs of shock was encountered occasionally This hypotensive phase after acute myocardial infarction has been noted by others[22] If clinical signs of shock did not develop the outcome did not appear to be affected adversely in the present series A few of this group of patients with hypotension had blood pressure readings as low as 80 or occasionally slightly lower However aside from some chest pain they remained [illegible] comfortable and warm were not cyanotic did not perspire their color remained good and shock did not follow This hypotensive response was not accompanied by evidences of severe cardiac insufficiency and in most of these patients the blood pressure returned

Table II Results of treatment of shock in acute myocardial infarction

Total number of patients	58	
Total number of deaths	29	50%
Total number of survivors	29	50%
Total number of deaths with adequate treatment	25	46%
Pressor effect	47	8[illegible]

[illegible] Excluding [illegible] th[illegible] th[illegible] vasop[illegible] th[illegible] [illegible] therapy

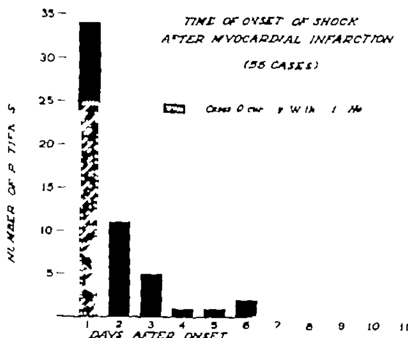


Fig. 1. Time of onset of shock after development of myocardial infarction.

toward normal during the latter part of their hospital stay. This group of patients was not included in the present study as suffering from shock and did not appear to have the same prognosis and outlook.

Premonitory shock. Shock which occurred after myocardial infarction did not always arise *de novo*. One of the striking features of the present study was the occurrence of one or more warning episodes of transitory shock followed by a return of the blood pressure to normal. These premonitory episodes developed one to several hours before deep shock supervened and were usually only temporary in nature, lasting from several minutes to an hour or two. In many of these instances the blood pressure returned to normal spontaneously without any specific vasopressor therapy. In a few patients small amounts of mephentermine sufficed to abolish the brief period of shock. In these patients typical signs of shock were present and these clinical signs served to distinguish this group from the previously described group of patients who exhibited only hypotension without other stigmata of the shock state.

This early transitory state of shock was a striking feature and preceded the development of deep shock in a significant number (36 per cent) of the patients. The spontaneous return of blood pressure levels to normal after such brief periods of shock suggested the operation of a homeostatic mechanism to maintain adequate perfusion pressure in the various organ systems and to preserve body circulation. The prognostic significance of this early hypodynamic phase of the circulation in acute myocardial infarction in predicting the subsequent occurrence of persistent shock is of obvious importance. It frequently appeared to be a warning sign of impending acute circulatory collapse.

Classification of cases. Frank clinical shock with all of its characteristic manifestations was present in all of the patients included in the present series. No patient with mild shock or hypotension alone was included in this group. However, it was possible to separate the patient further into three main groups on the basis of their clinical features and response to therapy. These groups were classified as follows: moderately severe, severe, and fatal. The primary criterion used in differentiating these groups was the response to therapy.

MODERATELY SEVERE SHOCK. The patients with moderately severe shock responded promptly to adequate vasopressor therapy and exhibited a rapid elevation of blood

pressure to normal levels accompanied by a fairly rapid abolition of the clinical signs of shock. These patients did not require the prolonged use of levarterenol by vein and usually within a period of 24 hours vasopressor agents could be discontinued *without further deleterious effects*. Anuria was uncommon. Oliguria was seen occasionally but prompt resumption of adequate flow of urine occurred with therapy. An example of the findings and problems encountered in such a patient is given in the following case history.

Case history. A 52 year-old white man who had sustained previous myocardial infarction 6 years ago developed severe substernal pain which radiated into the left arm and neck. His blood pressure during the episode of pain at home was 200/128 mm Hg (Fig. 2). On admission to the hospital he was in acute distress and had an ashen color. His blood pressure was 130/80 mm Hg; the pulse was of good quality. The cardiac rhythm was regular with a rate of 64 per minute; no gallop sound or murmurs were noted. An electrocardiogram on admission revealed deep Q waves in Leads II and III with S-T-segment elevation confirmed in Lead V. His subsequent tracings revealed the typical evolutionary changes of an acute posterior myocardial infarction.

Three and one fourth hours after admission he became cold and clammy and perspired profusely; his pulse became weak and the blood pressure dropped to 80/50 mm Hg. An infusion of mephentermine sulfate was started and within a few minutes his blood pressure returned to normal. His blood pressure then remained within normal limits and no signs of shock occurred for approximately 8 hours after the infusion was discontinued. He then developed pallor, weakness and dyspnea with blood pressure of 70/56 mm Hg. A second infusion of mephentermine was begun. When his blood pressure did not rise promptly an intravenous infusion of levarterenol bitartrate was initiated and this resulted in a rapid rise of his blood pressure to normal with disappearance of the signs of shock. The infusion was continued for 14 hours and then terminated, following which his blood pressure remained normal. No evidences of pulmonary edema appeared. His subsequent hospital course was uneventful and he was discharged in good condition.

COMMENT. This patient exhibited early shock of mild degree which originally was abolished promptly by the use of mephentermine. He subsequently developed deeper and more persistent shock which did not respond to mephentermine and necessitated the use of levarterenol. A prompt pressor response with the latter medication occurred; no evidence of congestive failure or arrhythmias appeared and the output of urine remained adequate.

SEVERE SHOCK. The group of patients with severe shock often required a prolonged period of vasopressor therapy. Many of these patients developed frank clinical congestive heart failure during this period of time, necessitating digitalization. However, with careful therapy adequate homeostasis was eventually achieved, the vasopressor substances were gradually discontinued and the patients survived.

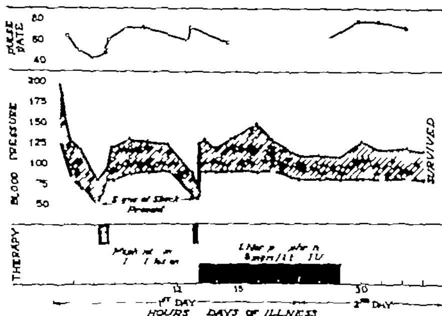


Fig. 2. Fifty two-year old man. MI severe shock after myocardial infarction (see text).

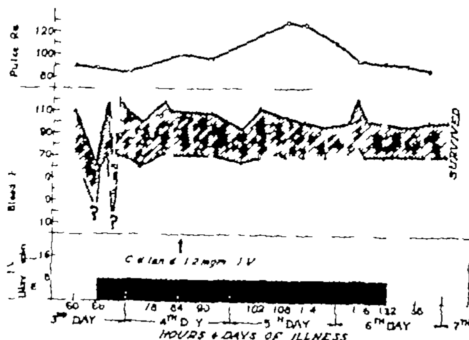


Fig 3 Sixty year-old man Severe shock Ac my ocard l infarct on (see text)

Oliguria w s frequent but with adequate therapy secretion of urine w s generally resumed although sometimes it w s diminished for variable periods An illustration of the clinical course and therapeutic problems is shown in the following case history

Case history A 60 year-old white m n developed severe nt rior best pain 65 l ours before entering the hospit il When seen t h ome by hi physician 3 hours before hospit lizati n his blood pressure f und t be 110/68 mm Hg nd his heart ate w 90 p minute Sh rtly bef re enterin the hospital he sudd nly became w ak nd on dmi on w found t be c ld l mmy p le and pe pirmg w th bl od pres ure of 62/ mm Hg (Fig 3) A regular cardiac rhythm with t of 88 pe minut w present no murmurs r gall p soun l w re heard The heart sound were f t The l ngs were clear thout rales Electrocardiographic tudie g ve findings con i tent with a recent posterior my cardi l infarction plu sign of n old nteroseptl myoc rdi l infarct Normal sinus rhythm was present

H r g en 8 mg f le arterenol bitartrate in liter f 5 per cent glucose by tra enous infusion Bl od pressure rose t n rm l lev l how er during the first 6 hours of h hospital stay he did n t secrete any urine Subsequently h outp t of urine w sat fact ry On the secon l m rning f his hospital t y he d lop d sign f congestive f ilure with rale in the lung bases nd d tent n of the ns in the neck At this time he w gi en Cedil nid 1 2 mg intra n u ly a d subsequently w s given digitoxin rally s re i ired The infusion f le art re l in l glucose w s ntinued for 64 hours until mid y the sixth d y t which time it was discontinued The p tient subsequent hospit l course w s smooth nd hi con alescence une ent ful

COMMENT Th p tie t w dmitted in deep shock nd bec me anuric for several hours Hi re ponse t sopressor ther py s tisfact ry lth ugh he sub equently devel pe l ongestiv fail re The prolong d administ t on of l norepinephrine required s well the use of digit lis These measures gradually resulted i return of hi hem dynamic st t tow rd normal with eventual recovery

FATAL SHOCK In the group of patient who succumbed to shock it w s frequ ntly difficult to elevate the blood pressure to adequate levels even with the use of hi h concentrations of v sopressor subst nces These patients in a group often exhibited continued signs of shock (such as sweating cy nosis weakness pallor and mental con fusion) even when the level of blood pres sure was maintained adequately by v so pressor subst nces There w s a high inci dence of congestive heart failure with pul monary edema in this group necessitating the frequent employment of digitalis glyco sides Their output of urine w s generally inadequate oliguria w s common and anuria also was frequently seen The pa tients in the group of fatalities revealed physical sign (such as very small volume pulse) comp tible with a profound fall in

cardiac output as well as with an inability of the homeostatic vasoconstrictor mechanisms to maintain adequate blood pressure and coronary flow. Some of the patients of this group also exhibited marked elevations in the serum glutamic oxalacetic transaminase level. Severe elevations in the transaminase levels have been ascribed in part to the effect of shock upon the liver rather than to cardiac damage alone.[34] A typical case history of a patient who succumbed to shock is outlined below.

Case history. Two days prior to admission this 59 year old white woman developed anterior chest pain associated with nausea and vomiting. The pain persisted in mild degree during the succeeding 2 days. Early on the morning of her admission to the hospital she suddenly became weak, restless and cold and clammy. At that time she was examined at home by her physician, who found her blood pressure to be 70/? mm. Hg. On admission to the hospital she was in deep shock and was sweating, pale and semiresponsive. Her heart rate was found to be 120 (Fig. 4) per minute with regular rhythm. The heart sounds were weak, but no murmurs were heard. The lungs were clear without râles.

Difficulty was encountered in finding a vein for infusion and she was given methoxamine hydrochloride 20 mg. intramuscularly without response. Her blood pressure shortly became unobtainable. A polyethylene catheter was inserted into the femoral vein and levarterenol was given in a concentration of 24 mg. per liter. This was subsequently increased to 32 mg. per liter. A brief pressor response was obtained but it was not sustained. Within 6 hours after she had been admitted moist râles appeared in both lung fields and spread extensively; dyspnea was evident. She was digitalized with 1.6 mg. of Cedilanid given by slow intravenous administration and oxygen was given continuously. Clinical signs of shock persisted throughout her hospital stay and she lapsed into coma. One hundred cubic centimeters of concentrated urine were obtained by catheterization 2 hours after her admission. Subsequently the patient became anuric and remained so until death.

Postmortem examination was obtained and revealed thrombotic occlusion of the anterior descending branch of the left coronary artery with recent anteroseptal infarction of the left ventricle. Pulmonary edema was also present with associated hydrothorax.

COMMENT. This patient exhibited the features of severe shock with a progressive downhill course and failure of response to large amounts of l-norepinephrine plus rapid digitalization. She became anuric, comatose and developed severe congestive failure with pulmonary edema. No satisfactory or sustained pressor reaction was obtained, the clinical signs of shock were never relieved and adequate homeostasis was never achieved.

Prognostic differentiation—surviving and fatal cases

Various clinical features of the survivors and of those who succumbed are listed in Table III.

Response to therapy. In estimating the prognosis one of the most dependable indications of survival was the promptness and

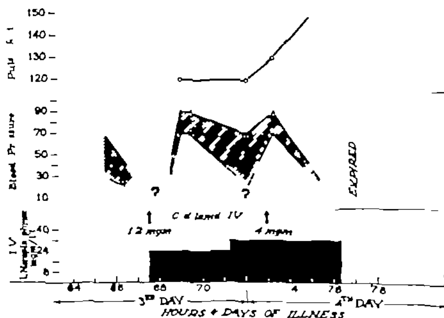


Fig. 4. Fifty-nine-year-old woman. Fatal shock after myocardial infarction (see text).

Table III. Clinical features of surviving and fatal cases

	Survivors	*Fatal cases*
Number of patients	29	25
Adequate pressor response	29 Patients (100%)	18 Patients (72%)
Output of urine (after therapy)	*Adequate*	*Oliguria or anuria*
Vasopressor administration rate	Good response to low rate	High rate needed
Time delay before treatment (average)	0.7 hr	2.6 hr
Arrhythmias	*6 Patients (21%)*	*10 Patients (40%)*
Congestive failure	11 Patients (38%)	16 Patients (64%)
Average age	58.6	64.5 yr
Average transaminase level	125 SGOT units *(16 patients)*	182 SGOT units *(12 patients)*

completeness with which shock was reversed by treatment, especially with the use of adequate vasopressor therapy. A prompt return of blood pressure to normal levels accompanied by the disappearance of clinical signs of shock was generally a favorable omen. The contrary was also generally true. However, some patients survived after the prolonged use of antipressor agents. The presence of oliguria or anuria indicating poor renal perfusion was likewise a prognostic sign of considerable importance, since patients who remained completely anuric after vasopressor therapy uniformly had a fatal course.

Rate of administration of levarterenol. The rate of administration of levarterenol needed to achieve a pressor effect, as has been noted by others,[1,4] was a prognostic sign of considerable value. In general, those patients who needed very large amounts of levarterenol per unit of time to secure an adequate pressor response generally failed to survive the episode. In the present series the maximum concentration of levarterenol bitartrate employed with subsequent survival was 32 mg. per liter; one patient who required this concentration lived. All of the other surviving patients responded to lesser concentrations of levarterenol.

In one instance 72 mg. of levarterenol bitartrate were given in one liter of solution in an effort to achieve adequate vasopressor effect; this did not result in the patient's survival. Survival has, however, been reported occasionally after the use of high concentrations of l-norepinephrine.[18] Thus, the requisite rate of administration of vasopressor substances needed to produce an elevation in blood pressure was an *important factor in an assessment of the prognosis,* and the patients in whom a rapid rate of administration of a relatively large amount of levarterenol was needed to maintain their blood pressure generally had a poor outlook.

Duration of shock before therapy. The duration of shock before treatment varied markedly in this series. The shortest duration of shock prior to treatment was less than a quarter of an hour; the longest duration, in a patient whose religious scruples delayed treatment, was 18 hours.

The time elapsed before the institution of adequate treatment was of great importance. In the surviving group (Table IV) the average time before adequate vasopressor therapy was instituted was less than 1 hour. In the patients who succumbed to shock the average period before treatment was instituted was 2.6 hours. None of the patients in whom treatment for shock was delayed for over 2½ hours survived. *By contrast, the great majority* of patients who survived received adequate vasopressor therapy within an hour after the onset of shock. When treatment was begun within 2 hours (Table V), the mortality rate was 40 per cent. In those patients in whom treatment was delayed more than 2 hours the mortality rate was 78 per cent. Sampson and Zipser,[19] Miller and Moser,[1] Griffith and associates,[3] and other investigators[6,17] have also reported a sharp rise in the mortality rate when

Table IV. Time elapsed before vasopressor therapy for shock was begun (54 cases)

	Survivors	*Fatal cases*
Number of patients	29	25
Total hours before treatment was begun	19.7	65.5
Average hours before treatment was begun		2.6

Table V. Mortality rate compared with interval before vasopressor therapy was begun (54 cases)

	Number of patients	Survivors	Deaths	Mortality (%)
Treatment begun within 2 hr	45	27	18	40
Treatment begun after 2 hr	9	2	7	78

there is a delay in the treatment of shock after myocardial infarction.

Arrhythmias. Severe arrhythmias were encountered more frequently in the patients who died (Table III). Thus 40 per cent of the patients who succumbed to shock developed arrhythmias, whereas only 21 per cent of the patients who survived developed arrhythmias. Complete heart block and ventricular tachycardia both were prognostic signs of grave nature and, when they persisted for any considerable period of time, were associated with a high mortality rate in this series of patients.

Congestive failure. Congestive failure occurred more frequently (Table III) in those patients who succumbed to shock. Moreover, when it developed, it was accompanied by a higher rate of mortality—59.2 per cent—than that occurring in those patients who did not develop failure and in whom the mortality rate was found to be 29.6 per cent (Table VI). Thus congestive failure when it developed was often an indication of grave cardiac insufficiency and when severe frequently indicated a serious prognosis. It should be noted, however, that some of the patients who developed congestive failure improved after the institution of adequate digitalis therapy and survived the episode of shock.

Age. It will be seen with reference to Table I that, although 2 patients in the ninth decade survived the episodes of shock, in general the mortality rate rose in the older age groups. Thus in the fifth decade the mortality was only 20 per cent, whereas in the eighth decade the mortality had risen to 85 per cent. Age therefore would seem to be a pertinent factor in an estimation of the outlook for survival.

Treatment

The mounting mortality rate with the passage of time clearly indicated that shock after myocardial infarction should be treated as a medical emergency with the least possible delay. Symptomatic therapy, such as the use of analgesics, elevation of the foot of the bed, and oxygen, relieved the premonitory shock promptly in some patients. However, in all cases of persistent shock, vasoconstrictor agents were utilized. Previous reports have shown that the use of transfusions and intravenous fluids, including plasma, does not decrease the mortality rate of shock when employed alone.[4] In the group of 54 patients who received adequate therapy, levarterenol was given in 48 cases. Metaraminol was given alone in 4 patients. In one patient, phenylephrine was given by slow intravenous infusion over a period of 18½ hours with satisfactory elevation of the blood pressure and the survival of the patient. In 10 patients, generally prior to beginning l-norepinephrine or metaraminol, mephentermine was given for variable periods of time. L-norepinephrine was the vasopressor agent of choice and was administered in the concentration and at the rate needed to effect an adequate vasopressor response. In this series the longest duration of treatment with l-norepinephrine following which the patient survived was 113½ hours.

In an attempt to detect shock promptly, the blood pressure and heart rate were often determined at intervals of an hour or two for the first 2 or 3 days of hospitalization. If shock persisted for more than a short period, levarterenol bitartrate was generally given intravenously, beginning with a concentration of 8 to 16 mg. per 1,000 c.c. of solution. The rate of administration was governed by the blood pres-

Table VI. Congestive failure in shock after myocardial infarction (54 cases)

	Number of patients	Deaths	Mortality (%)
Congestive failure present	27	16	59.2
Congestive failure absent	7	8	29.6

Table VII. Shock after myocardial infarction. Results of digitalization (54 cases)

Digitalis	Total cases	Survivors	Deaths	Mortality (%)
Digitalized	34	16	18	53
Not digitalized	20	13	7	35

sure and varied from 6 to as many as 40 or more drops per minute. This concentration was increased as needed to produce an adequate rise in blood pressure. It appeared preferable to keep the blood pressure in the neighborhood of 100 to 110 mm. Hg systolic. Marked elevations in blood pressure were avoided in order to prevent increased cardiac work in the presence of a damaged myocardium. When shock was severe and prolonged administration of vasopressor agents necessary, use was made of a polyethylene catheter ...ed into the deep veins. No definite evidence of aggravation of congestive failure due to vasopressor therapy was observed.

Since many of the patients with severe shock developed congestive heart failure, digitalis was frequently administered. Reference to Table VII reveals that the mortality was higher in patients who received digitalis. Usually in actual practice, however, digitalis was given in the most severe cases, and as would be expected, these patients had a high fatality rate. However, digitalis was often useful in controlling the symptoms of congestive failure and probably was responsible for aiding in the recovery of many of the surviving patients. The intravenous administration of Cedilanid was usually employed in this series, although rapid oral digitalization was occasionally used.

The development of arrhythmias occasionally complicated the shock state; these included complete heart block, auricular flutter and fibrillation, and episodes of tachycardia, both of auricular and ventricular origin. When persistent, unless quickly treated by appropriate means, these arrhythmias led to further deterioration of the cardiac status and to deepening of shock. In one instance, ventricular fibrillation developed in a patient in severe shock. Defibrillation by means of electroshock was successfully accomplished (utilizing an external defibrillator) with subsequent spontaneous return to normal sinus rhythm and survival of the patient. Oscilloscopic monitoring of the cardiac rhythm was occasionally utilized during critical stages of shock and was of aid in evaluating and planning therapy.

Discussion

Several studies have clarified the hemodynamics of patients with shock after myocardial infarction. Freis reported a profound reduction in stroke volume and cardiac index associated with the development of tachycardia and usually accompanied by an increase in peripheral resistance. He postulated that neurogenic reflexes of a compensatory nature produced the tachycardia and the increase in peripheral resistance.

Gilbert and his co-workers, Smith and associates, and Gammill and his co-workers have corroborated Freis' findings of a profound fall in cardiac output and stroke volume after cardiogenic shock. Lee has also confirmed the profound fall in cardiac output in patients with shock after myocardial infarction. These studies have also generally shown an increase in peripheral resistance, although in some instances peripheral resistance failed to rise. Agress, Binder and co-workers have indicated that when a compensatory rise in total peripheral resistance fails to occur, shock may develop after myocardial infarction. These latter workers have suggested the possibility of an inhibitory reflex arising in the damaged myocardium which prevents the rise in peripheral resistance in the presence of a diminished cardiac output.

Corday and associates have pointed out the importance of diminished arterial blood pressure in decreasing coronary flow and the reversibility of this effect when l-norepinephrine is employed. They have also shown that shock produces a selective fall in blood flow in areas of poor coronary circulation, resulting in a lack of contractility of the heart muscle in these region in experimental animals.[7] Restoration of blood pressure to normal resulted in a

return of normal contractility of these areas of heart muscle

The classic experiments of Wiggers[43] in animals indicate that irreversible circulatory failure may occur when hemorrhagic shock is prolonged for an extensive period. Sivranoglu and associates[44] have shown that after an hour sustained tissue anoxia in animals seems to produce myocardial damage of irreversible degree. In addition Calvin and his co-workers[46] have shown that the decreased availability of myocardial oxygen and the decrease in effective coronary flow which occur in shock can be reversed readily by restoration of blood pressures to normal with levarterenol. Corroboration of the effects of persistent shock in these animal studies is seen in the present series of patients in whom prolonged delay in the institution of therapy appeared to be lethal in almost all cases.

It thus appears from the results of the present study, as well as from the above cited laboratory investigations, that a critical time factor exists which must not be exceeded if survival is to be expected when shock occurs after a myocardial infarction. If inadequate coronary flow persists for a prolonged period of time, irreparable weakening of the myocardium occurs. Prompt abolition of shock and the maintenance of adequate perfusion pressure and coronary flow are therefore of paramount importance if the patient is to survive the episode of myocardial infarction.

Summary and conclusions

1 In 714 patients with proved acute myocardial infarction shock developed in 58 cases, an incidence of 8 per cent. The characteristic clinical features of this group of 58 patients was reviewed and various factors affecting the prognosis were evaluated.

2 The majority of cases of shock after acute myocardial infarction developed within the first 72 hours.

3 In 54 patients who received adequate treatment with vasopressor substances the mortality rate was 46 per cent. This was definite improvement over previously reported series treated by nonspecific measures in which the mortality rates ranged from 70 to above 90 per cent.

4 Premonitory shock, which was transitory in nature, developed in 36 per cent of the patients and was later followed by persistent shock.

5 Among the factors affecting the prognosis the duration of shock before treatment was of crucial importance. When adequate vasopressor therapy was begun within 2 hours the mortality rate was 40 per cent; when therapy was delayed over 2 hours the mortality rate mounted to 78 per cent. No patient in this series survived when treatment was delayed over 2½ hours.

6 Lack of prompt response to vasopressor therapy, severe congestive failure, the development of persistent arrhythmias, and anuria were all prognostic signs of grave importance.

7 The importance of early recognition and prompt treatment of shock after myocardial infarction was evident.

The author wishes to express his appreciation to Mrs David A Herfort, Record Librarian, Baylor Medical Center, and to the members of her staff for their assistance in this study.

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Table VII Shock after myocardial infarction Results of digitalization (54 cases)

Digitalis	*Total cases*	*Survival*	*Death*	*Mortality (%)*
Digitalized	34	16	18	53
Not digitalized	20	13	7	35

sure and varied from 6 to as many as 40 or more drops per minute This concentration was increased as needed to produce an adequate rise in blood pressure It appeared preferable to keep the blood pressure in the neighborhood of 100 to 110 mm Hg systolic Marked elevations in blood pressure were avoided in order to prevent increased cardiac work in the presence of a damaged myocardium When shock was severe and prolonged administration of vasopressor agents necessary use was made of a polyethylene catheter passed into the deep veins No definite evidence of aggravation of congestive failure due to vasopressor therapy was observed

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The vectorcardiogram in interatrial septal defect and persistent atrioventricular canal

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There are many problems concerning interatrial septal defect (IASD) and persistent atrioventricular canal (PAVC) which still have to be clarified from the vectorcardiographic point of view in spite of a number of papers published on the subject.[1-4]

In the present study we will consider some problems which in our opinion are of great importance. These are (1) whether there is any relationship between the rotation and morphology of the QRS loop in the horizontal plane (HP) and the right ventricular systolic pressure (RVSP), (2) whether in the case of IASD there is any conduction disturbance in the right bundle branch, and (3) the eventual value of the vectorcardiogram (VCG) in the differential diagnosis between IASD (of the ostium secundum type), PAVC, and other congenital defects.

Material and methods

Material. The VCG of 45 patients with defects of the interatrial septum were analyzed. On the basis of the diagnosis of the anomaly the cases were classified into three groups: Group I: IASD of the ostium secundum type—34 cases; among these were 8 cases of partial anomalous drainage of the pulmonary veins into the right auricle. Group II: IASD of the ostium secundum type associated with rheumatic alteration of the mitral valve—2 cases; one of these was a case of pure mitral stenosis and the other was a case of double lesion with marked predominance of insufficiency. Group III: PAVC—9 cases; 5 were the total form of PAVC and 4 were the partial form.

The diagnosis of the cardiopathy was based on clinical, roentgenologic, electrocardiographic, and hemodynamic data and was confirmed by operation under direct vision in all of the patients except 2 in Group III. In these 2 patients the diagnosis of the malformation was confirmed by necropsy.

The patients ranged in age from 5 to 46 years. Thirty were females and fifteen were males.

Methods. The VCG were registered using Grishman's cube system and a Sanborn Viso-Scope apparatus. The vectorcardiographic loop was modulated and interrupted 400 times per second.

F[illegible] th[illegible] D[illegible]partm[illegible]nt [illegible] M[illegible] [illegible] Pt[illegible] 1[illegible] Cl[illegible] [illegible] Paulo [illegible]
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Table I. Rotation of QRSsÊ in each plane

Group	Horizontal plane			Frontal plane			Sagittal plane		
	CW	8	CCW	CW	8	CCW	CW	8	CCW
I	20	12	2	25	9	–	–	18	16
II	2	—	–	2	–	–	–	—	2
III	2	3	4	—	2	7	3	6	—

CW: Clockwise. 8: Figure of eight. CCW: Counterclockwise.

Results

The rotation of the QRSsÊ in each plane is summarized in Table I.

Group I. Among the 20 cases (Fig. 1) in which there was a QRSsÊ with clockwise rotation in the HP throughout the extent of the loop, 17 of them showed predominance of the portion directed to the left and only 3 showed predominance of the portion directed forward and to the right (Fig. 2). The 12 cases with a *figure of-eight* inscription in the HP showed a clockwise rotated terminal portion directed forward and to the right (Fig. 3). The 2 cases with counterclockwise rotation throughout the extent of the QRS loop showed a great preterminal and terminal delay directed forward and to the right (Fig. 4). Besides these 2 cases, delays were registered in 18 others among which there were 8 of the preterminal and terminal type (Fig. 1), 9 exclusively terminal, and 1 exclusively preterminal. Seven cases showed terminal portions directed upward, rightward, and forward; these, however, were of small magnitude. Nevertheless, in 2 cases (6 per cent) the QRSsÊ was totally directed upward, forward, and to the right (Fig. 5).

The TsÊ was oriented to the left in all of the cases and backward and downward in 19 cases. In general, the backward and leftward deviation was not too marked (Fig. 1).

Relating the morphology and rotation of the QRSsÊ to the systolic pressure in the right ventricle, with the exception of the 2 cases in which there was counterclockwise rotation throughout the extent of the QRS loop in the HP, we found that: (1) in cases in which the portion of the loop which was directed forward and rightward was of small magnitude, the mean RVSP was 41.5 mm Hg, varying from 30 to 46 mm Hg in 19 cases and from 50 to 55 mm Hg in the other 5 cases; and (2) in cases in which there was important deviation of the loop forward and to the right (8 cases) the RVSP ranged from 42 to 69 mm Hg (average 58 mm Hg).

Group II. The first case in this group, a case of IASD associated with mitral stenosis, also showed predominance of the *leftward-directed portion over the forward* and rightward directed portion that had a clear preterminal delay. In the second case (Fig. 6), a case of IASD associated with predominant mitral insufficiency, the HP inscription showed a slightly delayed preterminal appendix with a counterclockwise rotation and a predominant forward and rightward directed portion.

The TsÊ was oriented backward and to the left in both cases. The RVSP was 50 and 60 mm Hg, respectively.

Group III. The QRSsÊ was oriented *upward, forward, and to the right in all* cases of PAVC. In the 4 cases in which the rotation was counterclockwise in the HP an important forward and rightward directed portion with preterminal and terminal delay (Fig. 7) was registered. The 2 cases with clockwise rotation in the HP did not show any delay in the inscription of the loop (Fig. 8). In the other 3 cases in which there was a figure-of-eight inscription in the HP (Fig. 9), preterminal and terminal delay was registered in 2 cases and only preterminal delay in the third. It is interesting to note that in the frontal plane (FP) the rotation was counterclockwise in 7 cases, and that in the sagittal plane (SP) it was a figure-of-eight *inscription in 6 cases* and showed complex morphology in all cases.

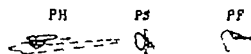


Fig 1 IASD of the ostium secundum type Clockwise rotation in the horizontal plane with RVSP of 35 mm. Hg Terminal delay i seen in the three planes



Fig 2 IASD of the ostium secundum type An important portion of the QRS-Ê loop is directed forward and to the right The RVSP 60 mm Hg



Fig 3 IASD of the ostium secundum type A figure-of-eight inscription is seen in the horizontal plane and terminal delay observed in both the horizontal and sagittal planes

The T-Ê was oriented downward backward and to the left in all the cases

The RVSP ranged from 30 to 100 mm Hg In the 2 cases with clockwise rotation throughout the extent of the loop in the HP the pressure was 70 and 83 mm Hg respectively

Comments

Group I In 20 cases of IASD of the ostium secundum type the diagnosis of right ventricular overload was made on the basis of the clockwise rotation in the HP[4] (Fig 1) In the other 12 cases in which the rotation was not clockwise throughout the extent of the loop (Fig 3) the configuration of the loop in the HP and especially the forward and rightward orientation of the terminal portion with clockwise rotation allowed us to establish the diagnosis of initial right ventricular overload[7] In reality this configuration of the QRS loop in the HP was observed in cases of regression of right ventricular enlargement in cardiopathies for which operation was performed under direct vision preceding the normalization of the vectorcardiographic curve

Relating the morphology and rotation of the QRS loop in the HP with the RVSP we found that there seems to be a certain relationship between the levels of pressure and the magnitude of the forward and rightward-directed portion of the loop as long as the conduction disturbance is not very important

In our experience an important fact was the difference in behavior of the QRS-Ê in the HP in cases of IASD (volume overload) and in cases of pure pulmonary stenosis (barrier overload) Thus in cases of IASD with slightly increased or even

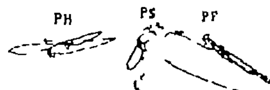


Fig 4 IASD of the ostium secundum type VCG of the complete RBBB type counterclockwise rotation in the horizontal plane with preterminal and terminal delay directed forward and to the right

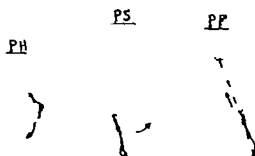


Fig 5 IASD of the ostium secundum type The QRS-Ê is directed upward and to the right completely Note the predominantly clockwise rotation in the frontal plane

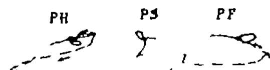


Fig 6 IASD of the ostium secundum type associated with double mitral lesion Observe the lack of the upward-directed portion of the QRS loop

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As can be seen this type of bundle branch block is relatively rare (present in 6 per cent of the cases) and some authors such as Burch [4] after electrocardiographic studies do not admit the existence of complete RBBB in IASD These authors believe that the QRS complexes with duration of 0 12 second or greater are representative of right ventricular hypertrophy occurring mainly in aged patients Our 2 patients with complete RBBB were 12 and 32 years of age respectively Both patients underwent operation but in spite of the normalization of the heart area and right ventricular pressure no vectorcardiographic modifications were registered in posterior studies [9]

The persistence of the morphology of complete RBBB in cases of IASD which had been completely corrected by operation suggests definite conduction disturbance probably of congenital origin

Group II The VCG of the case in which there was association of IASD with mitral stenosis was similar to the VCG of the cases of Group I In the second patient who had IASD associated with predominant mitral insufficiency the VCG showed a delayed preterminal portion with counterclockwise rotation in the HP suggesting a conduction disturbance in the right branch accompanying right ventricular overload these facts might have hindered the appearance of the signs of left ventricular enlargement It should be noted that in this case the VCG did not show upward and rightward orientation as in PAVC

Group III No vectorcardiographic differences were observed between the partial and total forms of PAVC Complete RBBB was registered more frequently in PAVC than in IASD being present in 4 cases (45 per cent) (Fig 7) In the other 5 cases there was evidence of right ventricular overload associated with left ventricular overload and in 3 cases intraventricular conduction disturbance was registered (Fig 9)

In all of our cases the most constant vectorcardiographic finding was the marked deviation of the QRSsÊ loop upward and to the right even in cases with high RVSP (100 mm Hg) this fact has already been observed by several authors [14] This peculiar orientation of the QRS loop (upward) has been related to left ventricular overload which is anatomically true in the case of PAVC and to the hypertrophy of the basal portions in which case a possibly smaller quantity of Purkinje fibers might contribute to a delay in the progress of the stimulus In our opinion it is very probable that these two factors are of importance since all of our cases showed marked left ventricular enlargement on x ray examination and 7 of our cases showed rather evident delays in the vectorcardiogram

The vectorcardiographic pattern of PAVC The analysis of our material allows us to establish that in the majority of cases of PAVC the vectorcardiograms tend to show a uniform behavior characterized by the following elements (1) marked deviation of the QRSsÊ loop upward and to the right (100 per cent of the cases) (2) presence of the morphology of complete RBBB (45 per cent of the cases) (3) figure of eight rotation in the sagittal plane with complex morphology (65 per cent of the cases) (4) counterclockwise rotation in the frontal plane (80 per cent of the cases) (5) counterclockwise or figure of-eight rotation in the horizontal plane (80 per cent of the cases)

Differential diagnosis between PAVC and other cardiopathies with similar vectorcardiographic behavior According to our experience vectorcardiographic features (QRSsÊ loop oriented upward and to the right) similar to those observed in PAVC have been found in the following cardiopathies chronic Chagas myocarditis myocardiosclerosis and less frequently congenital anomalies Among the latter we have to consider IASD of the septum secundum type in 7 5 per cent (Fig 5) and pure interventricular septal defect (IVSD) in 20 per cent of our cases (Fig 10) It is our opinion that even in cases of IASD in which the QRS loop is directed upward and to the right some elements may facilitate the differential diagnosis with PAVC These elements are (1) Conduction disturbance of the complete RBBB type is rare in IASD (2) The rotation of the QRS loop in the frontal plane was clockwise or figure of-eight in the great majority of cases of IASD (3) The rotation in the horizontal plane was clockwise in all cases of IASD

Summary

Thirty six cases of inter trial septal de fect (IASD) of the septum secundum type (2 of these cases howed association of rheumatic alteration of the mitral valve) and 9 cases of persistent atrioventricular canal (PAVC) were studied from the vectorcardiogr iphic point of view

Attention is drawn to the following points (1) clockwise rot ttion in the hori zontal plane in IASD of the septum secun dum type in spite of normal or slightly elevated right ventricular systolic pressure (2) high incidence of intraventricular con duction disturbance (55 per cent of the cases of IASD) (3) persistence of the morphology of complete right bundle branch block (RBBB) in the VCG in cases of isolated IASD after surgical correction of the defect and normalization of the cardiac area and of pressure in the right ventricle (4) value of the VCG in the diagnosis of PAVC and (5) vectorcardio-graphic data for the differential diagnosis between PAVC and isolated IASD (of the septum secundum type) and interven tricular septal defect (IVSD) with the QRSsÊ loop oriented upward and to the ght

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Differentiation of massive pericardial effusion from cardiac dilatation using I^{131} albumin

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The differentiation of massive pericardial effusion from cardiac dilatation is frequently difficult, even when a thorough diagnostic study including routine roentgen techniques is carried out. To illustrate this problem, x-ray films from 6 patients with enlargement of the cardiac shadow are illustrated in Fig. 1. Films numbered *1*, *2*, and *3* are from patients in whom cardiac dilatation was the principal lesion, whereas films numbered *4*, *5*, and *6* are from patients with massive pericardial effusion. The close similarity of films 1 and 4, 2 and 5, and 3 and 6 is apparent. Angiocardiography will permit ready differentiation, but this procedure is not without risk. Cardiac catheterization and the injection of carbon dioxide as a gas contrast medium have also been utilized to make this distinction. Recently, a radioisotope technique for the estimation of the intracardiac blood volume has been described. This is based on the use of intravenously injected I^{131} albumin which remains in the vascular system long enough to become essentially equally distributed in the circulating blood. The blood volume of the organ could be calculated if its total radioactivity could be measured accurately and compared to the radioactivity of a unit volume of circulating blood. In the case of the heart, the volume of blood in its chambers is large compared to that in the coronary vascular bed. Therefore, this approach measures essentially intracavitary blood. By comparing the intracardiac blood volume calculated by this method to the area of the cardiac shadow, it is possible to detect a large pericardial effusion. In the presence of pericardial effusion, the intracardiac blood volume is normal and the heart shadow is greatly enlarged. Cardiac dilatation, on the other hand, produces a large intracavitary volume and a proportionately large cardiac shadow.

Materials and methods

Eight hospitalized patients with large cardiac shadows on the teleoroentgenogram were studied by the same technique described previously in 41 patients.[4] Of the 49 patients, 7 had pericardial effusion confirmed by pericardiocentesis or at autopsy. Their diagnoses were: tuberculous pericarditis, 2; metastatic carcinoma to

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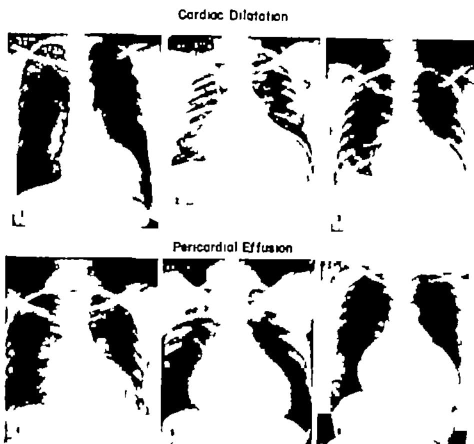


Fig. 1. Comparison of cardiac shadows in cardiac dilatation and pericardial effusion.

pericardium 2, disseminated lupus erythematosus 1, chronic glomerulonephritis 1, and mediastinitis with pericarditis 1. The diagnosis of pericardial effusion was made clinically but not confirmed in an additional patient with lupus erythematosus. During treatment with corticosteroids the heart shadow of this patient rapidly returned to normal. This patient is represented by circle *A* in Fig. 2.

The dimensions of the heart shadow were determined fluoroscopically in each patient. The cardiophrenic angles and two points immediately below the pulmonary artery on opposite borders of the cardiac shadow were projected to the anterior chest wall. A four-sided paper pattern was constructed corresponding to these four points. Lead shielding was placed around the margins of the paper pattern to prevent detection of radioactivity in the lungs and great vessels in so far as possible. Corrections were made in the size of this pattern so that it was reduced in size to allow for the fact that shielding was placed between the crystal and the heart rather than around the edges of the heart. A heavily shielded 2 by 2 inch cylindrical NaI crystal was placed 25 cm. from the anterior chest wall over the center of the heart. Scintillation pulses corresponding to energies below 0.15 Mev. were eliminated by a spectrometer. The precordial radioactivity was recorded after allowing 10 minutes to elapse after the injection of 50 to 100 μc of I^{131} albumin into an arm vein. Venous blood was collected into a tube containing dry heparin at this time. From this sample the hematocrit was determined by centrifugation at 2,000 RCF. The hematocrit was corrected for 3 per cent trapped intercellular plasma. Plasma radioactivity was measured as previously described.[7] Radioactivity of whole blood was calculated using the corrected hematocrit.

An I^{131} albumin standard was counted within a tissue phantom made of masonite to determine the mean counting rate of 1

μc of I^{131} albumin within the normal human heart This counting rate was then related to the counting rate of 1 μc of I^{131} albumin obtained with the Geiger Muller tube employed in measurements of whole blood For these particular counters the Geiger Muller tube recorded 166 times as many counts per microcurie of I^{131} albumin as did the precordial probe Thus the intracardiac blood volume is equal to

$$\frac{\text{Precordial radioactivity (cpm)}}{\text{Whole blood radioactivity (cpm/ml)}} \times 166$$

The factor 166 is based on normal sized hearts In 4 of the patients with enlarged hearts individual calibration factors were obtained The resulting figures were 145 153 154 and 168 These differences were believed to be minor The factor 166 was used for calculation in all patients

Results and interpretations

The intracardiac blood volume of all patients was plotted against the area of the precordium monitored (Fig 2) There is an approximate linear relationship between the area monitored and the calculated intracardiac blood volume in the normal subjects and in patients with heart disease Of 8 patients known to have pericardial effusion 5 had a normal intracardiac blood volume of less than 800 ml and a large heart shadow Of the other 3 2 were found to have cardiac dilatation at autopsy (*B* and *C*) In one of these (*C*) cardiac dilatation was the predominant lesion the pericardial effusion totaled approximately 100 ml The third subject (*D*) survived so that the presence or absence of cardiac dilatation could not be determined by pathologic examination

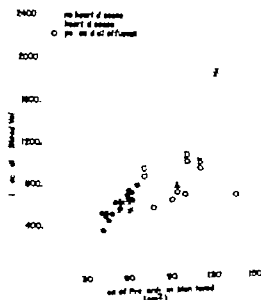


Fig 2 Relationship of intracardiac blood volume to area of cardiac silhouette

Discussion

Errors inherent in the measurement of the intracardiac blood volume by the present technique have been previously discussed Accuracy might be significantly improved by using more satisfactory methods for outlining the cardiac shadow with shielding and by determining calibration factors for the individual patients Scintograms of the heart may also be used to determine the presence of pericardial effusion[3] but the apparatus necessary is more complex than that required for the estimation of the intracardiac blood volume The experience to date is not sufficient to establish the reliability of present techniques but the results clearly indicate that this is a sound approach to the clinical diagnosis of pericardial effusion

Summary

1 An isotope technique for the measurement of intracardiac blood volume has been used to detect massive pericardial effusion

2 An outstanding feature of this procedure is its simple and innocuous nature

3 In 5 patients with pericardial effusion and normal hearts the cardiac shadows were enlarged whereas the intracardiac blood volumes were normal

4 The results indicate that this is a sound approach to the clinical diagnosis of pericardial effusion

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Disability absenteeism of industrial workers with myocardial infarcts

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The physician who wishes to rehabilitate patients who have recovered satisfactorily after myocardial infarction must recognize a number of deterrents. Among these are fear that the individual will have another attack for which the employer may be held liable and concern that the cardiac employee cannot work effectively and that he will experience high and costly sickness absenteeism.

The administration of compensation benefits for workers who experience subsequent attacks is a complex process which often involves courts, commissions, and customs wherein the testimony and opinions of the individual practitioner of cardiology seemingly carry little weight. For removal of this obstacle to cardiac rehabilitation, legal and socioeconomic reforms would seem to take precedence over strictly medical advances.

On the other hand, the effectiveness on the job of cardiac workers who are placed in a suitable assignment has been demonstrated so widely and overwhelmingly that the productivity of such employees is no longer of major concern. In this study, data which pertain to the absenteeism experience of industrial workers with proved myocardial infarcts are presented. Such information, which heretofore has received scant attention, may be helpful to physicians in discussing return to work situations with patients and employers alike.

Method

The 100 subjects whose records form the basis of this report were selected from current or recent lists of permanently partially disabled employees identified in the total population of 7,500 workers of a large oil refinery and petro-chemical plant. The two criteria required for inclusion in the study were: (1) the worker must have a diagnosis of healed myocardial infarction established beyond reasonable doubt, after which (2) he must have resumed work for a period of at least a year. (Data collected on subjects whose period of work was 6 to 12 months did not differ significantly from the findings to be presented; however, subjects with less than a year of work experience after infarction were excluded in order to avoid the possible criticism that the period of observation at work was too short.) All have been effective workers on the job since they were included in an organized program for the selective placement of handicapped workers which entailed periodic review by both physician and supervisor. The average age of the study group was 50 years as compared to 45 years for the entire worker population.

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Complete information as to the number of absences from work due to disability, the duration of each absence, and the clinical reason for each absence was collected for each of the 100 subjects. The survey period began with the patient's return to work after an initial myocardial infarction and ended June 30, 1960. Seven subjects in the study group became totally and permanently incapacitated for work and 3 died. For these individuals the survey period ended on the last day on which they worked.

Some patients experienced subsequent infarcts and again resumed work for a year or more. The periods of absence from the job due to later attacks are included in the analysis. Only five infarcts in this series were "silent" or unrecognized in the acute stage. These were discovered usually at routine periodic examination, when stable electrocardiographic patterns typical of healed infarction were found on individuals whose previous tracings were normal. Such findings were not associated with periods of disability.

The absenteeism experience of the 100 workers with proved myocardial infarcts is compared with data for the whole refinery population derived in a similar manner for those years in which most of the cardiac cases were analyzed. Each period of absence is measured in calendar days, and rates are calculated according to the procedure recommended by the American Medical Association Committee on Medical Care for Industrial Workers.

Other matters concerned with heart disease and employment have been excluded as irrelevant to the study of absenteeism.

Results

The 100 subjects of this study had an average of 4.7 years (range, 1 to 17 years) at work after the initial episode of myocardial infarction. Thus, 470 man-years of work experience are included in the survey. Ten workers subsequently developed a second infarct and 2 patients had a third. In all, 112 infarctions were recognized in the subjects during the study.

Disability absenteeism rates for the cardiac workers are compared with rates for all refinery workers in Table I. The worker with a healed infarct was absent 10.0 calendar days annually because of sickness or injury (disability rate) as compared to an average of 9.9 days for all refinery workers. The annual number of absences per employee (frequency rate) for the cardiac group was 1.2 and for all workers 1.1. The average duration of absence (severity rate) was 8.3 days for the study group and 8.9 days for the whole worker population.

Only 2.7 of the 10 days of absence each year by the cardiac worker were the result of cardiovascular disease. The major types of cardiovascular disabilities occurring in the 100 subjects are shown in Table II. Chest pain due to angina, coronary insufficiency, or myocardial infarction accounted for two to three times as many days of disability as did either myocardial failure or other conditions (arrhythmias, strokes, hypertension, peripheral vascular disease, and time away from the job for observation and regulation of medication). The frequency rate for cardiovascular absences was 0.16 and the severity rate was 17 days.

Analysis of absenteeism by age group (Table III) reveals variation in cardiovascular absences from 2.2 days per year for the 50-54 age group to 4.7 days for the 45-49 age group. The increase in noncardiovascular absences in workers in the 60-64 age group was caused by a number of prolonged periods of disability involving operations.

Table IV compares the absenteeism experience of salaried employees and wage earners. The salaried group was composed of 16 supervisory and technical and 26 clerical workers, 42 in number, with an observed work experience of 210 man-years. The wage earners consisted of 39 skilled and 19 unskilled employees, a total of 58, with 260 man-years at work after infarction. Cardiovascular absences for the salaried workers averaged 1 day per worker annually, as compared to 4 days for the wage earner. All types of disabilities for the salaried employee amounted to 6.7 days yearly, about half the number of days (12.7) lost by the wage employee. Corresponding disability rates for these groups in the entire population were 6.1 and 11.6.

In addition to disability and frequency rates, the duration of absence for an episode of acute myocardial infarction is

Table I Disability absenteeism experience

Employee group	Disability rate (days/employee/yr)	Frequency rate (absences/employee/yr)	Severity rate (days/absence)
Workers with healed infarcts (100 employees)	10 0	1 2	8 3
All refinery workers (7 500 employees)	9 9	1 1	8 9

Table II Cardiovascular causes of disability for work in 100 employees with healed infarcts

Cause of absence	Disability rate (days/employee/yr)	Frequency rate (absences/employee/yr)	Severity rate (days/absence)
Chest pain	1 5	0 07	21
Myocardial failure	0 5	0 0	
Other (arrhythmia etc)	0 7	0 07	10
All cardiovascular	2 7	0 16	17

Table III Absenteeism experience by age group

Age group (yr)	Number of workers	Number of infarcts	Work experience (man years)	Disability rate (days/employee/yr) Cardiovascular	Other	Total
40–44	13	14	52	2 3	5 6	7 9
45–49	14	16	63	4 7	5 2	9 9
50–54	18	18	97	2 2	4 2	6 4
55–59	31	36	136	2 8	5 4	8 2
60–64	24	28	1 2	3 4	13 9	17 3

Table IV Absenteeism of salaried employees and wage earners

Employee group	100 Workers with healed myocardial infarcts: Disability rate (days/employee/yr) Cardiovascular	Other	Total	Frequency rate (absences/employee/yr) Cardiovascular	Other	Total	Average days lost with new infarcts	All refinery workers: Disability rate (days/employee/yr)
Salaried (4 workers)	1 0	5 7	6 7	0 1	1 06	1 18	93	6 1
Wage (58 workers)	4 1	8 6	1 7	0 18	1 08	1 26	109	11 6

shown. This was 93 days for the salaried worker and 109 days for the wage earner; the combined average was 102 days.

Discussion

These data suggest that patients with myocardial infarction who are able to return to work in a suitable assignment do not have high disability absenteeism. The 100 subjects with a total observed experience of 470 man years on resuming work after an infarction averaged only 10.0 calendar days of disability annually. In comparison, the average for all refinery workers was 9.9 days. The survey group also had surprisingly low frequency rates for disability absences—0.16 for cardiovascular causes and 1.2 for all causes.

These findings are in general agreement with other reports on absenteeism of full-time workers with heart disease of various etiologies. One hundred and eighty-nine workers followed by the Work Classification Unit, Adult Cardiac Clinic of the Third (New York University) Medical Division, Bellevue Hospital, lost an average of approximately 9 days per year.[3] Greer[4] reported an average absenteeism of 13.3 days annually for 45 industrial workers with arteriosclerotic heart disease compared with 11.3 days for all employees. Neither report described details of the derivation of data upon which conclusions were based.

Wyshak, Snegireff, and Law[5] studied absenteeism of workers with various types of heart disease or diabetes in 17 manufacturing plants[6] and found that employees with coronary heart disease were able to work with little more disability than persons free of heart disease; cardiac workers placed in "light" jobs lost less time than "production" workers.

A previous study from this department also revealed a generally good prognosis for patients who returned to work after cardiovascular absences.[6] Nearly 88 per cent of those who resumed work either continued on the job or retired for nonmedical reasons. In the course of the 3 year observation period, approximately 6 per cent died and another 6 per cent retired for medical reasons. This analysis, based on a large number of cardiovascular absences of all types, differs from the present one, which is based on the experience of patient employees with a specific type of heart disease.

It may appear surprising that the employees of this study who had established heart disease of a serious nature did not lose more time from the job because of disability than did the average worker. It is possible that such employees, having recovered satisfactorily from a life-threatening illness to resume a productive job in industry, are highly motivated to stay on the job and avoid unnecessary absences. Even though higher job motivation may be contributory to the lower absenteeism experience of salaried workers as compared to wage earners, other important factors are the generally better work environment and less physically demanding assignments available to the "white collar" worker.

It deserves re-emphasis that disability absenteeism is affected by many factors, nonmedical as well as medical.[7] For example, it has long been recognized that some periods of apparent disability bear a strong relationship to the availability and duration of disability payments. None of the workers who were surveyed was involved in a compensation suit. All were covered by a company benefit plan which provided, in general, full pay for the first 12 weeks of disability and one-half pay for an additional 40 weeks. Such a plan offers sufficient economic security to generally deter efforts to work when actually disabled, and joint follow-up of each absentee by full-time company physicians and the personal physician tended to minimize unnecessary and unduly prolonged periods of absence.

Summary

Disability absenteeism of 100 subjects who resumed industrial work for an observed 470 man years after myocardial infarction is reviewed. They experienced 10.0 calendar days of disability per person annually, whereas the average for all workers in the same plant was 9.9 days. Only 2.7 days of absence each year were due to cardiovascular conditions. The cardiac employee had on the average 1.2 period of disability yearly, as compared to 1.1 absence per worker for the whole refinery population. Analysis of absenteeism by age

group revealed no significant trend in the patients studied Salaried cardiac workers had one fourth as many days of absence for cardiovascular reasons and one half as many days of disability for all reasons as did wage earners

The absenteeism experience of workers with healed myocardial infarcts who resumed work in a suitable job assignment did not differ significantly from that of the whole plant population

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Marked left axis deviation

Indication of cardiac abnormality

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Left axis deviation is a common electrocardiographic finding yet opinion as to its significance has varied considerably ranging from normal variant to definite evidence of cardiac disease This has been due in large part to a lack of uniformity in definition It has been considered present by some when the mean QRS axis is no more leftward than +30 degrees Others have defined it as at least −30 degrees leftward orientation of the axis It has been pointed out [1-4] that left ward deviation of −30 degrees or more (LAD) is usually associated with cardiac disease This observation has been minimized by the lax use of the term left axis deviation and is often ignored particularly in an otherwise normal electrocardiogram

The factors considered to cause left axis deviation have included altered anatomic and electrical position of the heart emphysema left bundle branch block left ventricular hypertrophy myocardial fibrosis and unknown factors associated with aging Left ventricular hypertrophy has been considered to be the most common cause Grant[1] proposed that LAD is usually due to myocardial fibrosis either patchy involvement in the distal intraventricular network (parietal block) or more proximally by myocardial infarction (peri infarction block) He found a wide angle between the mean initial 0 04 second and mean terminal QRS vectors in the latter and thought that with LAD an angle that exceeded 100 degrees might be helpful in diagnosing anterolateral myocardial infarction even in the absence of diagnostic Q waves

Intrigued by Grant's concept and impressed by the frequency with which this electrocardiographic finding has been encountered at the Veterans Administration Hospital Houston Texas we undertook this study

Methods

The electrocardiograms of all patients who died in this hospital during a 10 year period were surveyed Of approximately 2 500 patients 252 were found whose electrocardiograms showed the mean QRS axis to be directed between −30 and −90

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Table I Diagnosis of 154 patients at necropsy

Diagnosis	Normal QRS duration		Prolonged QRS duration		Total
	Emphysema		Emphysema		
	With	Without	With	Without	
With myocardial infarction					
Normal mean initial vector	3	6	2	5	16
Abnormal mean initial vector					
Diaphragmatic	3	9	1	5	18
Anterolateral with peri-infarction block	1	5	1	11	18
Otherwise abnormal	3	5	2	5	15
Without myocardial infarction					
Right ventricular hypertrophy	6	0	0	0	6
Valvular disease	0	1	0	3	4
Hypertensive heart disease	2	10	4	4	20
Arteriosclerotic heart disease	13	4	1	3	21
Idiopathic fibrosis	7	5	0	0	12
Miscellaneous	0	2	0	1	3
No heart disease	0	3	0	0	3
Bundle branch block					
Right					
With infarction	0	1	1	1	3
Without infarction	0	0	2	3	5
Left					
With infarction	0	0	3	5	8
Without infarction	0	0	0	2	2

*One additional patient who had no evidence of heart disease is listed as having right bundle branch block without infarction.

degrees (LAD). Lesser degrees of leftward deviation were not investigated. Ninety-eight patients could not be studied because necropsy was not performed or because the hearts or clinical records could not be examined. The report deals with the other 154 patients.

Mean vectors were determined for the total QRS duration, the initial 0.04 second of the QRS, and for the remainder of the QRS (mean terminal vector). Particular attention was given to the lateral wall of the left ventricle on both gross and microscopic examination. The weight of the heart was considered to be the most reliable index of left ventricular hypertrophy.

The 154 patients were separated into 2 groups containing those with normal QRS duration (0.09 second or less in the standard limb leads) and those with prolonged QRS duration. The 2 groups were further separated as seen in Table I. The patients with myocardial infarction were categorized according to the direction of the mean initial 0.04 second QRS vector. Good correlation existed between the electrical and anatomic position of the infarction.

The term "anterolateral infarction with peri-infarction block" was used to designate only those cases in which the mean initial 0.04 second QRS vector was directed between +90 and +180 degrees. A diagnosis of arteriosclerotic heart disease included only those patients with angina pectoris or in whom moderate to marked sclerosis of the coronary artery was found at necropsy. A diagnosis of idiopathic myocardial fibrosis applied only to those patients with fibrosis but no clinical evidence of heart disease and no more than minimal sclerosis of the coronary artery. No patient was listed in more than one category. Emphysema was accepted as having existed when such a diagnosis had been made either

Table II. Diagnosis of 100 living patients with LAD

Diagnosis	With clinical heart disease		Without clinical heart disease		Total
	LAD only	LAD plus other ECG abnormality	LAD only	LAD plus other ECG abnormality	
With myocardial infarction					
Normal mean initial vector	1	1	—	—	2
Abnormal mean initial vector					
Diaphragmatic		2	—	2	4
Anterolateral with peri-infarction block	–	2	—	2	4
Otherwise abnormal	–	4	—	7	11
Without myocardial infarction					
Right ventricular hypertrophy		–	—	—	0
Valvular disease	–	3	—	—	3
Hypertensive heart disease	1	4	2	1	8
Arteriosclerotic heart disease	3	7	—	—	10
Idiopathic fibrosis			—	—	0
Miscellaneous	5	7	—	7	19
No heart disease			21	10	31
Bundle branch block					
Right			—	3	3
Left		3	—	2	5

Table III. Age by decades of 154 patients at necropsy and of 100 consecutive living patients with LAD

	Fourth	Fifth	Sixth	Seventh	Over seventh	Total
Necropsy	4	20	37	69	24	154
Living	4	6	8	59	23	100

clinically or at necropsy. We have some reservations as to the reliability of these criteria for the diagnosis of emphysema.

A series of 100 consecutive living patients with LAD was also studied (Table II). These patients were encountered in a 4-month period during which time electrocardiograms were recorded on approximately 600 patients. The 2 patients with myocardial infarction and normal mean initial 0.04-second vector had had diagnostic clinical courses and electrocardiograms during previous hospitalizations. Arteriosclerotic heart disease was used to designate only those patients with angina pectoris. The miscellaneous group was comprised of 12 patients who had cardiomegaly or heart failure that was not clearly due to the other listed causes and 7 patients with electrocardiographic changes of left ventricular hypertrophy or strain as the only evidence of cardiac disease.

Results

All of the patients were male. This was attributed to the almost exclusively male population of the hospital. Only 4 patients were younger than 40 years (Table III). One of these had a myocardial infarction, 1 had malignant hypertension, and 2 had idiopathic myocardial fibrosis.

Myocardial infarction was present in 80 of the 154 patients (52 per cent). Of the 136 patients without bundle branch block

65 had myocardial infarction. Three of the 8 patients with right and 8 of 10 patients with left bundle branch block had myocardial infarction. Twenty-six of the 80 patients with myocardial infarction did not have a history of infarction. Eighteen of these 26 patients also had nondiagnostic electrocardiograms including 1 with right and 4 with left bundle branch block.

The 2 patients with left bundle branch block without myocardial infarction had aortic stenosis. Five patients with right bundle branch block did not have myocardial infarction. One patient had angina pectoris, 2 had aortic insufficiency, and 1 had no clinical evidence of cardiac disease but did have a mild increase in heart weight. The fifth patient had no evidence of cardiac disease clinically or at necropsy.

There were 69 patients who had neither myocardial infarction nor bundle branch block (Table I). The 6 patients with right ventricular hypertrophy had clinical cor pulmonale. There were 4 patients listed in the valvular disease group. An additional 8 patients had valvular disease, 6 of whom also had myocardial infarction or angina pectoris and 2 of whom had left bundle branch block. Aortic stenosis or insufficiency was present in 11 patients and mitral insufficiency in 1 patient. All patients in the group with idiopathic myocardial fibrosis demonstrated mild fibrosis except 1 in whom it was marked (Table IV). The weights of the heart were normal or only slightly increased (Table V).

In the miscellaneous group the patient with the prolonged QRS had scleroderma with extensive cardiac and pulmonary involvement. The second patient had recurrent myocarditis of unknown etiology. The third patient had a Grade 2 apical systolic murmur as the only clinical manifestation of heart disease. Necropsy disclosed mild fibrosis and mild increase in the weight of the heart as the only cardiac abnormalities.

Four patients had no evidence of cardiac abnormality clinically or at necropsy. One was included in the group that had right bundle branch block. One patient had nonspecific T wave abnormalities and 1 had prolongation of the Q-T interval. The fourth patient, who died of a progressive chorea of undetermined etiology, was found at necropsy to have extensive fatty infiltration of the myocardium. We were reluctant to attribute the LAD to the infiltration.

Fifty-five patients were thought to have emphysema. The distribution of these patients in each of the diagnostic categories is presented in Table I.

QRS prolongation greater than 0.09 second was present in 65 patients. Seventeen had bundle branch block. Of the patients without bundle branch block, myocardial infarction was present in 32 of 48 patients with prolonged QRS duration in contrast to 35 of 88 with normal QRS duration. Generally, those with prolongation had greater heart weights. The degree of fibrosis varied widely in those with QRS prolongation but only 5 had none. Duration of the QRS varied from 0.10 to 0.20 second. Duration exceeding 0.12 second occurred exclusively in those patients with left bundle branch block and in those with anterolateral myocardial infarction and peri-infarction block. No relationship could be demonstrated between the QRS duration and weight of the heart, thickness of the myocardium, or degree of fibrosis.

Heart weight and fibrosis (Tables IV and V) could be correlated with the diagnostic categories as might be expected, that is, generally greater heart weights in patients with hypertensive and valvular disease and generally more fibrosis in patients with coronary artery disease. Myocardial fibrosis was diffuse and no particular involvement of the anterolateral wall of the left ventricle was observed.

The vector angle was wide in two categories: (a) patients with anterolateral myocardial infarction with peri-infarction block by criteria of selection and (b) patients with right bundle branch block. The vector angle was narrow in those patients with diaphragmatic myocardial infarction and in those with left bundle branch block. With these exceptions, the vector angle could not be correlated with diagnosis, weight of the heart, or extent of fibrosis. Emphysema has been stated to widen the vector angle. If known instances of emphysema were excluded, no correlation could be found between the vector angle and the presence or absence of myocardial infarction.

Table II Diagnosis of 100 living patients with LAD

Diagnosis	*With clinical heart disease*		*Without clinical heart disease*		*Total*
	LAD only	*LAD plus other ECG abnormality*	*LAD only*	*LAD plus other ECG abnormality*	
With myocardial infarction					
Normal mean initial vector	1	1	—	—	2
Abnormal mean initial vector					
Diaphragmatic	–	2	—	2	4
Anterolateral with peri-infarction block	–	2	—	2	4
Otherwise abnormal		4	—	7	11
Without myocardial infarction					
Right ventricular hypertrophy	–	–	—	—	0
Valvular disease		3	—	—	3
Hypertensive heart disease	1	4	2	1	8
Arteriosclerotic heart disease	3	7	—	—	10
Idiopathic fibrosis			—	—	0
Miscellaneous	5	7	—	7	19
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Bundle branch block					
Right		–	—	3	3
Left		3	—	2	5

Table III Age by decades of 154 patients at necropsy and of 100 consecutive living patients with LAD

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clinically or at necropsy We have some reservations as to the reliability of these criteria for the diagnosis of emphysema

A series of 100 consecutive living patients with LAD was also studied (Table II) These patients were encountered in a 4-month period during which time electrocardiograms were recorded on approximately 600 patients The 2 patients with myocardial infarction and normal mean initial 0 04 second vector had had diagnostic clinical courses and electrocardiograms during previous hospitalizations

Arteriosclerotic heart disease was used to designate only those patients with angina pectoris *The miscellaneous group* was comprised of 12 patients who had cardiomegaly or heart failure that was not clearly due to the other listed causes and 7 patients with electrocardiographic changes of left ventricular hypertrophy or strain as the only evidence of cardiac disease

Results

All of the patients were male This was attributed to the almost exclusively male population of the hospital Only 4 patients were younger than 40 years (Table III) One of these had a myocardial infarction 1 *had malignant hypertension and 2 had* idiopathic myocardial fibrosis

Myocardial infarction was present in 80 of the 154 *patients (52 per cent)* Of the 136 patients without bundle branch block

to have diabetes mellitus of 8 years duration. The average age of the living patients was slightly greater than that of those in whom necropsy was performed (Table III).

Because of the infrequency of young patients in both series, the electrocardiograms of 100 consecutive patients under 40 years of age were reviewed. LAD was present in 2 patients, one with a previous myocardial infarction and the other with heart failure of undetermined etiology.

Discussion

The results of this study support the experience of others that, with rare exception, left axis deviation of greater than −30 degrees is electrocardiographic evidence of cardiac abnormality. There were only 4 patients (2.6 per cent) of the 154 at necropsy who had no evidence of cardiac abnormality clinically or at necropsy.

This study did not decisively answer the question of whether left ventricular hypertrophy or myocardial fibrosis was the principal etiological factor of LAD. The number of patients without fibrosis (13 per cent) was similar to the number without increase in the weight of the heart (17 per cent). The occurrence of mild fibrosis and mild increase in the weight of the heart was also nearly equal, 24 and 23 per cent. The observation that myocardial infarction was present in 52 per cent of the patients and unequivocal coronary artery disease in an additional 13 per cent suggested that myocardial fibrosis was the more important factor.

The valvular disease group was interesting not only because of its small size but because of the type of lesion encountered: aortic stenosis or insufficiency in 11. These lesions usually cause left ventricular hypertrophy. They also are associated commonly with disturbances in coronary circulation. Indeed, 5 of the patients had either angina pectoris or myocardial infarction. The single instance of mitral disease was as

Table V Heart weights of 154 patients at necropsy

Diagnosis	Normal QRS duration: Less than 350 grams	350 to 450 grams	450 to 600 grams	Over 600 grams	Prolonged QRS duration: Less than 350 grams	350 to 450 grams	450 to 600 grams	Over 600 grams
With myocardial infarction								
Normal mean initial vector	3	1	4	1	–	1	5	1
Abnormal mean initial vector								
Diaphragmatic	3	2	5	2	–	2	3	1
Anterolateral with peri-infarction block	3		2	1		1	1	1
Otherwise abnormal		4	1	1		2	2	1
Without myocardial infarction								
Right ventricular hypertrophy	4	1	1		–			
Valvular disease			1		–	3		
Hypertensive heart disease		4	8		–	1		
Arteriosclerotic heart disease	5	5	5		–		1	1
Idiopathic fibrosis	5	7			–		2	2
Miscellaneous		1		1	–			
No heart disease	3			–	–	–		1
Bundle branch block								
Right								
With infarction				1				
Without infarction			–	–		–		
Left					1	2		
With infarction	–		–					
Without infarction	–		–					

sociated with marked sclerosis of the coronary artery

The authors have some reluctance in using the term emphysema in view of some of the newer concepts of the disease However the usual frame of reference during the survey period implied over distention of the lungs Although emphysema was frequent in the subjects of this study there were only 6 patients in whom it occurred in the absence of either left ventricular fibrosis or hypertrophy All 6 had marked right ventricular hypertrophy and clinical cor pulmonale It would seem that emphysema alone rarely causes LAD

The frequency of reported emphysema was remarkably similar in the patients with bundle branch block (33 per cent) myocardial infarction (24 per cent) and in those with QRS prolongation (23 per cent) In the patients with none of these the frequency was 53 per cent They were characterized by generally smaller heart weights and degrees of fibrosis This distribution may be simply fortuitous but introduces another possible mechanism for the production of LAD mild left ventricular fibrosis or hypertrophy may cause some leftward deviation of the electrical axis with emphysema producing further deviation to more than −30 degrees

Quite consistently in those patients with LAD and emphysema the electrocardiograms were characterized by small voltage in the limb leads and lateral precordial leads

The angle between the mean initial 0 04-second and mean terminal QRS vectors was found to be of little value in predicting the presence of myocardial infarction

The number of patients with left bundle branch block and LAD was too small to have statistical significance however it was of interest that 8 of 10 had myocardial infarction Right bundle branch block might be expected to result in LAD yet only 1 of 8 patients evidenced no cardiac abnormality

The series of 100 consecutive living patients was quite similar to the group of 154 patients in whom necropsy was performed in age distribution and in frequency of occurrence of all diagnostic categories with the notable exceptions of the group with myocardial infarction and that with no heart disease This discrepancy was probably more apparent than real had the true occurrence of occult myocardial infarction sclerosis of the coronary artery and idiopathic myocardial fibrosis been obtainable Such an assumption seems reasonable in view of the observation that approximately 30 per cent of the patients in whom myocardial infarction was found at necropsy had a negative history and slightly more than half of these had electrocardiograms which were not diagnostic of myocardial infarction Also of significance was the fact that 26 of the 31 patients with no apparent heart disease were 60 years of age or older

A review of the electrocardiograms of 100 consecutive patients under 40 years of age revealed only 2 with LAD One patient had had a myocardial infarction and the other had heart failure of undetermined etiology

No conclusions were drawn of the significance of LAD with reference to prognosis or cardiac functional capacity

Summary

The electrocardiograms of 154 patients with left axis deviation of the QRS of between −30 and −90 degrees (LAD) were correlated with the findings clinically and at necropsy Only 4 patients (2 6 per cent) did not have cardiac abnormality even though in 17 patients the electrocardiograms were normal except for the left axis deviation (LAD) Myocardial infarction was present in 52 per cent of the patients and unequivocal coronary artery disease in an additional 13 per cent The angle between the mean initial 0 04 second and mean terminal QRS vectors was of little value in predicting the presence of myocardial infarction Emphysema was thought to have only a contributory role in producing LAD The data on 100 consecutive living patients with LAD and on 100 consecutive living patients under 40 years of age were interpreted as affording additional support to the conclusion that LAD with rare exception is electrocardiographic evidence of cardiac abnormality

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Coronary heart disease and hypertension among Jews immigrated to Israel from the Atlas Mountain region of North Africa

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Investigations of the prevalence of coronary heart disease and hypertension as carried out in many countries have dealt mostly with populations that had been natives of their respective countries for many generations The diversity of population groups in Israel provides opportunities for such epidemiological research but in addition the factor of change in environment by migration may have to be taken into account

Research on coronary disease in this country has revealed on the one hand that it is comparatively rare among Oriental Jews particularly the Yemenites [1] but on the other hand that together with a rising mean level of cholesterol in the blood its incidence seems to increase with prolonged stay under the living conditions of Israel even in immigrant groups previously almost immune to the disease [2,3]

It seemed of interest to determine the prevalence of coronary heart disease and hypertension in a group of Jews who had recently immigrated to this country from the Atlas Mountain region of North Africa since almost all of them had exchanged a primitive environment for the atmosphere of a more advanced country Furthermore such a stock taking enquiry may facilitate future research undertaken to deal with the changes possibly evoked by such new and rather revolutionary conditions

The place chosen for this investigation was Asafah a settlement in the Northern Negev where about 3 200 people mostly derived from the region mentioned were housed at the time of immigration in 1957

These people are of Mediterranean stock this fact has also been borne out by a simultaneous blood group study [7] They are usually of medium body size and build A minority derive from the island of Gjerba located in continuation of the Atlas territory in the Bay of Tunisia in most features the people from Gjerba resemble the majority group described They were mostly craftsmen or peddlers in their native countries (Morocco Tunisia) their economic and living standard apparently had been very low At present they are engaged part time in farming or road building mostly as unskilled laborers Their families are of large size and their living conditions here also are mostly poor

Up to the time of this study in the

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summer 1959 they had not yet been well integrated into the social framework of this country and many had not yet even partly adopted the language of this country It seemed that their psychologic adjustment to the new environment was equally poor a situation by no means eased by their relative isolation and concentration among themselves

The following investigation has been carried out in order to establish to what extent coronary disease and hypertensive vascular disease are prevalent among these Atlas Jews

Material and methods

Both men and women the great majority of whom were over the age of 30 years have been examined Many of them were patients with minor injuries or ailments who applied to the local Sick Fund Clinic of which two of us have been in charge in subsequent turns (Y A and B K) others who were waiting for relatives to be taken care of or who were applying to the nearby labor exchange were invited to take part in this study

A short history mainly as to cardio vascular complaints was taken A physical examination was performed with particular attention to cardiac findings such as enlargement of the heart accentuation of the second aortic sound arrhythmias and signs of congestive heart failure A series of blood pressure readings were taken with the subjects in the supine position until the values became stable these final readings were recorded and used for evaluation

One hundred and six individuals in whom such casual but repeated blood pressure readings had been obtained were re-examined several months later the subjects were recalled at random with the purpose of evaluating the significance of such one time measurement

In a number of individuals electrocardiograms and samples of blood (103 and 134 cases respectively) were taken this number was determined by the degree of cooperation of the people examined as well as a certain limitation of facilities The selection of the individuals from whom blood or an electrocardiogram or both were to be taken was determined by purely practical considerations (i . an additional worker of the team shipping facilities etc) so that these examinations can be considered as samples taken at random After being refrigerated the samples of blood were sent to Jerusalem within at most 48 hours for analysis Blood cholesterol and levels of uric acid were determined Cholesterol was determined according to Keys and Anderson s modification of Abel s method Uric acid was determined according to Hepler and Stoss Kopf[9] by means of this method 100 normal adults showed a mean of 3 9 ± 0 57 mg per cent and only 3 per cent had values above 5 mg per cent

Blood from the samples collected was also used for a study of the blood group distribution in this community [7] In addition a food survey was conducted at the

Table I Age distribution of the individuals examined (Atlas Jews)

Age group (years)	*Males*	*Females*	*Total*
Less than 30	17	28	45
31–40	13	32	45
41 50	28	26	54
51–60	34	19	53
61 0	32	2	34
Over 70	2	1	3
Total	126	109	234

Table II Mean cholesterol values in various age groups (Atlas Jews)

	Males		*Females*	
Age group (years)	*Mean (mg)*	*Number of individual examined*	*Mean (mg)*	*Number of individual examined*
Less than 30	154 4	5	157 2	9
31–40	161 4	9	159 5	20
41 50	155 9	17	163 4	14
51–60	177 0	21	186 1	9
61 0	1 0 1	28	——	—
Over 0	——	2	——	—
Total		82		52
Mean cholesterol of total	16 8 ± 28 2		165	

Table III Findings in the nine abnormal electrocardiograms

Case number	Sex	Age (yr)	Blood pressure (mm Hg)	Clinical remarks	Electrocardiographic findings
24	M	57	135/80	—	Low voltage T isoelectric T $_{VL}$ low voltage left axis deviation
28	F	47	120/80	—	Horizontal heart low voltage of T aV$_L$
56	M	52	160/100	Rough systolic murmur over Erb point	Horizontal heart pronounced left ventricular strain pattern
72	M	68	135/80	Pulmonary emphysema	T low voltage T flat Q in aV$_L$
143	F	38	130/85	Soft systolic murmur over aorta	Significant Q in aV$_L$ but no other electrocardiographic abnormalities
165	M	62	180/120	Accentuated second aortic sound	Ventricular extrasystoles
192	M	74	185/85	Left ventricle enlarged	Symmetrical inversion of T T$_4$ $_L$T$_F$ Q in V$_L$ old anterolateral infarct
208	M	65	200/130	Left ventricle enlarged	Left bundle branch block
233	M	66	170/100	Pulmonary emphysema	Horizontal heart low voltage of T significant Q and high take off of S-T in aV supraventricular extrasystoles

same time Both studies will be reported upon separately [3] However it may be mentioned here that the daily intake of fat was found to be between 50 and 60 Gm

When an unexpectedly high prevalence of hypertension was discovered analyses of urine were made and 24 hour samples of urine were taken in a number of individuals in whom proper cooperation could be obtained for determination of sodium chloride excretion (flame photometer)

Results

One hundred and thirty men and 106 women 236 individuals in all were examined Table I shows their age distribution The average age of the men was 50 6 years that of the women was 38 5 years

The mean age of the 82 men in whom cholesterol and levels of blood uric acid were determined was 53 years the mean blood cholesterol value was 167 8 ± 38 2 mg per cent (range from 72 to 261 mg per cent) The mean level of blood uric acid was 4 67 ± 0 96 mg per cent (range from 1 71 to 6 93 mg per cent)

The mean age of the 52 women thus examined was 39 1 years The mean blood cholesterol was 165 ± 32 mg per cent (range from 99 to 226 mg per cent) The mean level of blood uric acid was 3 33 ± 0 04 mg per cent (range from 1 56 to 5 42 mg per cent) Table II shows the mean cholesterol values for both sexes according to age groups

Figs 1 4 show the systolic and diastolic blood pressure measurements for the men and women examined Out of the 236 people studied 52 individuals (22 per cent) —34 men (26 per cent) and 18 women (16 9 per cent)— had diastolic blood pressures of 95 mm Hg or more Consequently according to common standards 22 per cent of all the individuals examined have to be considered to be hypertensive If 90 mm Hg is taken as the lower limit of hypertension then 45 men and 34 women—33 per cent of all the individuals—have to be regarded as hypertensive individuals

Table III reviews the electrocardiographic findings which may be considered as abnormal in 3 cases (Nos 2 192 233) the presence of ischemic heart disease is indicated The three individuals concerned are over 65 years of age

Discussion

The findings encountered in this population group can be summarized as follows The mean blood cholesterol values of men (167 8 mg per cent) and women (165 mg per cent) are low in comparison with those of many Western populations and are close to what has been found in more primitive populations in Africa [n] India [n] or in new immigrant Yemenites [3 4 ?] and

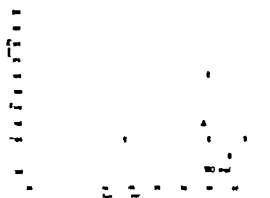


Fig 1 Systolic blood pressure values of 120 males studied in this investigation



Fig 2 Diastolic blood pressure values of 120 males studied in this investigation.

in Jews from Cochin[15] in this country A trend of the values to rise with age seems to be absent in our group The highest cholesterol level observed in this series was in a 64 year old hypertensive man (262 mg per cent)

The mean blood uric acid levels of 4 67 mg per cent in males and 3 33 mg per cent in females seem to be neither unusually low or high But it should be noted here that so far there seem to be no available figures derived from population or group surveys which would indicate the prevalence of hyperuricemia nor are there data for mean blood uric acid levels of populations apart from a rather high mean value of 5 03 ± 1 12 mg per cent for men and 4 05 ± 0 89 mg per cent for women recently obtained by us in an investigation of the Cochin Jews[15] We[16] have previously expressed the opinion as have others[17,18] that there seems to be a relationship between an increased level of uric acid and the occurrence of coronary heart disease Therefore we have so far included such determinations in surveys designed to study the causes of coronary disease and we intend to include them in the future

Coronary heart disease The determination of the presence and prevalence of coronary heart disease in a given group of individuals can at best be an estimate This estimate has to be based on the electrocardiographic evidence of myocardial infarction or cardiac ischemia it has to rely on the experience and observations of the examining physicians and has to take into account the number of cases of sudden deaths which have occurred under the highly suspect clinical picture of coronary

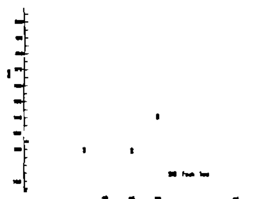


Fig 3 Systolic blood pressure values of 96 females studied in this investigation

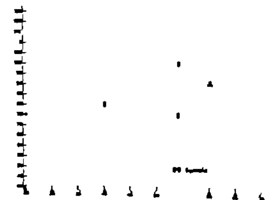


Fig 4 Diastolic blood pressure values of 96 f studied in this investigation

occlusion Extensive autopsy data—although rarely available—will be most valuable The finding of a low mean blood cholesterol in a population is today regarded by many as presumptive evidence of a low incidence of the disease in question whatever the mechanism of such a low level may be *Whether a low mean level* of uric acid justifies the same conclusion cannot yet be stated

In the light of these considerations the evidence at hand should then be examined

Two of us (Y A and B K) during a 2 year period in which we were the only physicians serving in turn this population have observed only two men who presented a clinical picture of myocardial infarction Both died Otherwise the two of us have not been called upon to see such a case nor have we heard of one in this community for the medical care of which we were responsible Among the many patients who have applied to the clinic only one presented a clear history of anginal pain This individual suffered from syphilis of the aorta Among the 9 electrocardiograms which showed any significant abnormalities one indicated clearly a past infarct of the heart two others exhibited Q waves in Lead aVL and changes of the S T interval in the same lead

When these scant observations and findings are taken together—possibly with the low mean level of blood cholesterol—the conclusion then becomes justified that coronary heart disease is infrequent among the population group examined

Hypertension Although the distribution curve of blood pressure measurements shows a bimodal shape and therefore suggests the existence of two types of populations normotensive and hypertensive subjects the present material does not seem adequate to enter into the controversy[13, 4] whether hypertensive blood pressure has to be considered as a continuation of normal blood pressure or whether it bears the characteristics of an a priori different state At any rate there are good reasons to assume that there is no single figure for diastolic blood pressure which will separate hypertensive from normal levels We therefore report our blood pressure measurements in Figs 1-4 so that these data can be independently evaluated with everyone using his own criteria as to what value or values discriminate between normal and high values Certainly to say that a certain pressure readin is the one that separates the normal from the elevated is at present impossible

Accepting with a slight modification the recommendation of the World Health Organization s subcommittee dealing with cardiovascular epidemiology[11] we consider that all individuals with a diastolic pressure of 95 mm Hg or above are hypertensive This appears to be the more justified since according to impressions gained from previous work[7] Oriental Jews when normal seem to have comparatively low blood pressures Consequently 22 per cent of the individuals examined here have to be regarded as hypertensive If 90 mm Hg were considered as the artificial line of separation the unusually high figure of 33 per cent would represent the number of hypertensive individuals

Even a 22 per cent prevalence of hypertension in a group of people over 30 years of age represents a conspicuously high figure Therefore it was considered necessary to take repeated measurements as outlined above (see Methods)

An attempt was made to evaluate the reliability of a one time determination of blood pressure as described above testing whether such a determination gives adequate information about the normotensive versus hypertensive state of a given individual The series of double measurements in 106 individuals who were recalled at random enabled us to examine these data by MacNemar s test for significance[2] Accordingly the difference in number of hypertensive individuals was found to be not significantly different as determined on the basis of one as against two examinations in the random group examined The number of conflicts between measurements was not above the expected figure It appears that we do face a true increase in the number of hypertensive individuals

Such a high percentage of individuals with elevated arterial pressure calls for an explanation Many people who belong to the community examined have told us that they regularly eat a great deal of salt this seem to hold true for their group in general *An enquiry conducted in their*

homes as well as in their food stores and at the clinic tends to confirm these statements. In addition 21 individuals who were chosen according to their willingness to cooperate were found to excrete from 8.75 to 21 Gm. of sodium chloride in 24 hours (mean 13.9 Gm.). These examinations were carried out in winter in order to obtain samples uninfluenced by excretion of sodium chloride in the sweat. These values seem rather high—16 men excreted more than 10 Gm. of sodium chloride per day and 7 among them excreted more than 15 Gm.—though not exceedingly so.

A large series of urine analyses as well as clinical experience among this group of people deny an unusual incidence of pyelonephritis as a source of hypertension.

To approach the problem from an entirely different angle it may be stated that these Moroccan and Tunisian communities have recently undergone great social changes which require considerable adaptation on the part of the individual. Of rural or semiurban origin in a part of their country far removed from Western civilization these people have been transferred into new competitive and puzzling surroundings and circumstances. Moreover a certain breakup of their social patterns and family cohesion seems to have occurred within recent years; previously the extended family, the isolated rural background, as well as strict adherence to religious tradition had kept these people within their customary age-old framework. Apparently this social structure had already been in a process of radical change and dissolution before the recent immigration of these people to Israel.

Impressions and evidence are recently forthcoming which indicate that in certain population groups atherosclerosis may well be dissociated from hypertension. So far this concerns mostly ethnic groups of African descent. In the British West Indies for instance a large incidence of hypertension has been observed—Humphries found that about 40 per cent of the natives of Nassau had a systolic blood pressure of over 150 mm. Hg. Moser found that over 50 per cent of West Indians who were more than 39 years of age had systolic pressures above 150 mm. Hg; about 30 to 40 per cent of all people over 40 years of age had diastolic pressures of 100 mm. Hg or more. Of those people over 40 years of age 60 to 70 per cent had a diastolic pressure of above 90 mm. Hg. In these Bahaman people the excretion of sodium chloride seemed to be about 12 Gm. per day on an average in a limited study. Moser and his co-workers[4] in their study of 3,594 Negro subjects in the Bahamas report that 25 per cent of the males had a blood pressure of 150/90 mm. Hg; for women the figure was 30 per cent. They have recently concluded from their data and those of others that hypertension is frequent among Negroes wherever they are and that to a certain extent its incidence is independent from the process of urbanization. Stuart[?] at a congress held in Jamaica in April 1960 again emphasized the high prevalence of hypertension in Jamaica and St. Kitts but also pointed out that bacilluria at least in elderly women was very frequent and might possibly be a partial explanation of this phenomenon by way of causing pyelonephritis. Dr. Dodu[29] from Ghana informed us that he has been impressed with the relative rarity of coronary occlusion, at least in the hospital wards in Accra (Ghana), whereas hypertension seems by no means to be rare in hospital patients there. Corcoran and his co-workers, in a short preliminary report on their investigations among a group of West Indian Negroes as studied in St. Kitts, West India, speak about the Negro's predisposition to hypertension, but stress at the same time the low prevalence of ischemic heart disease. Also in Japan, where in some village populations hypertension reaches a frequency of 30 per cent,[31] as well as in the South African Bantu,[32] hypertension seems to be frequent whereas ischemic heart disease is rarer than in Europe or in the United States. Schroeder[33] in a report on his cardiovascular itinerary through various Oriental countries describes hypertension as by no means rare in all locations where he visited.

All the information available so far—including the well-known tendency of the North American Negro to develop hypertensive cardiovascular disease—concerns by and large either Negro populations in various locations or the Japanese. ... the group which is investigated her

of Mediterranean stock as their physical make up and their blood group distribution clearly show stands isolated among other Mediterranean peoples as a new group comprised of many individuals with high blood pressure but apparently little affected at present by ischemic heart disease or at least affected to a much lesser extent than would be expected if this were a European or North American community with so high a prevalence of high blood pressure The ultimate meaning of a high blood pressure reading is whether it is compatible with good health and a normal life expectancy or in other words only such high pressures as those that indicate a future state of defective health or shorter life expectancy may be considered to be abnormal For this reason only longitudinal studies will clarify whether there is something like a normal range of blood pressure for the human race—of about 55 to 90 mm Hg diastolic—which is valid for all groups

Comparison with other groups multidisciplinary analysis of genetic and environmental determinants as well as a long term follow up of the newly immigrated group may elucidate some of the reasons for such an unusually high proportion of individuals with high blood pressure

Summary

Two hundred and thirty six adults newly immigrated to Israel from the Atlas Mountain region have been examined for coronary heart disease and hypertension

The mean blood cholesterol value in men was found to be 167 8 ± 38 2 mg per cent in women it was 165 ± 32 mg per cent The mean level of blood uric acid in men was 4 67 ± 0 96 mg per cent in women it was 3 33 ± 0 04 mg per cent

Although coronary heart disease seems to be infrequent among this ethnic group the number of people with high blood pressure was found to be unduly large 33 per cent had a diastolic blood pressure of 90 mm Hg and above 22 per cent had a diastolic pressure of 95 mm Hg and above

Recently population groups in which the prevalence of hypertension and coronary heart disease are dissociated have been described i e Negroes and Japanese The group of people of Mediterranean origin reported on here seems to show this same epidemiological phenomenon coronary heart disease is uncommon but hypertension is frequent

We are grateful to the following individuals who helped us in various ways to carry out this investigation Dr Shatal physician in charge of the Negev District General Labor Sick Fund Dr W W Caackes of the Laboratory of Clinical Research Hebrew University Hadassah Medical School who supervised the laboratory examinations Dr Henry Rosenfeld social anthropologist Hebrew University for his advice M Benjamin Bracha the office clerk of the Azata Sick Fund Clinic Mrs M Mion the nurse at that clinic and Miss Ruth Ben Zeev of Kibbutz Kfar Aza

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Myocardial infarction treated by early ambulation. Effect of prolonged anticoagulant therapy on the immediate prognosis after discharge from hospital

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In 1956 we published in this Journal a paper on the effect of early ambulation on the results of treatment of myocardial infarction. Since 1952 it has been the general principle in this hospital to permit patients with myocardial infarction to sit up in bed after the symptoms of shock have passed. Bedside toilet privileges have also been allowed at an early stage. In the absence of specific contraindications the patients have begun ambulation on an average 2 weeks after infarction—recently even earlier—and they have been discharged 1 week later. In other respects the usual treatment has been administered.

In the above mentioned series of patients treated in 1952-1954, the results were favorable with respect to the absence of complications during hospitalization. Thus during the first week of ambulation, which we regarded in advance as the most critical period in the early ambulation, there were only 2 sudden deaths and 1 recurrence in our series of 258 patients. However, during the first month after discharge the incidence of complications was relatively high. In the 236 patients followed up, 1 sudden death and 21 new infarcts occurred. Additionally, 8 patients were rehospitalized for chest pain, the cause of which, however, could not be ascribed to a new infarct. The incidence of complications during the first month after discharge from the hospital was high also in comparison to the following 5 months, during which 10 sudden deaths and 10 new infarcts occurred.

In the discussion in our previous paper we presented two possible explanations for the relatively high incidence of recurrences during the first month after discharge from hospital, suggesting that it was a result either of early ambulation or of discontinuance of anticoagulant therapy on discharge from the hospital. Since 1952 the majority of our patients with myocardial infarction have received phenylindandione as an anticoagulant during hospitalization, but only since 1957 has this treatment been continued after the patients were discharged from the hospital.

To obtain information concerning the effect of anticoagulant therapy on the high incidence of recurrence during the first month after discharge, we have studied the cases of myocardial infarction in this hospital in the latter half of 1957 and during 1958-1959.

Material

During this period a total of 565 patients with confirmed myocardial infarction were admitted to this hospital. During the

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similar period of 1952-1954 the cases totaled 332; thus the increase was 70 per cent. Although the increase has certainly been influenced to some extent by the increase in population and possibly by more sensitive diagnostic criteria, it appears from these figures that a real increase has occurred during this time. In the later series 127 patients, equivalent to 22.5 per cent of the series, died in the hospital before ambulation was begun. The mortality rate in the series of 1952-1954 was 22.4 per cent. Of the other 438 patients, 117 either received no anticoagulant therapy because of, for example, a complicating disease such as peptic ulcer or hypertension, or the therapy was discontinued after discharge because of a lack of appropriate laboratory facilities or because of poor cooperation by the patient. However, especially in severe cases, an attempt was made despite the difficulties to continue the treatment at home, at least during the immediate period after discharge. After exclusion of these two groups, 321 patients remained. In these 321 we observed the course of the disease during the first month after they were discharged, and it is this group which form the basis for the following report of results.

We shall first present certain data concerning the series. The figures in parentheses give the corresponding information for the series of 1952-1954.

Female patients numbered 58, or 18.1 per cent of the series (28.7 per cent), and their mean age was 61 (63) years. The mean age of the male patients was 56 (54) years and that of the whole series was 56 (57) years.

Using the criteria of Schnur, we grouped the patients as follows according to the severity of the disease: pathologic index rate 0-39, 210 patients = 65.4 per cent (60.5 per cent); pathologic index rate 40-79, 88 patients = 27.4 per cent (32.9 per cent); pathologic index rate 80-, 23 patients = 7.2 per cent (6.6 per cent).

On the basis of the electrocardiographic changes the infarct was diagnosed as anterior, anterolateral, or anteroseptal type in 193 patients, or in 60.2 per cent (60.0 per cent); posterior or posterolateral type in 107 patients, or in 33.3 per cent (29.0 per cent); purely lateral in 7 (5) patients, and purely septal in 2 (10) patients. Determination of the type was not possible in the other 12 (14) patients.

Confinement to bed averaged 12.0 (16.2) days, and the total period of hospitalization was 20.1 (22.6) days.

Complications during ambulation in hospital. Sudden death: In the present series there was 1 (2) case of sudden death; this was in a 58-year-old man who died on the third day of ambulation after hospitalization for 11 days. New myocardial infarction: There were 2 (1) cases of new myocardial infarction; both of the patients recovered. Congestive heart failure: Symptoms of heart failure developed in 10 (5) patients. The symptoms were mild and transient in 9 patients and severe in only 1 patient. Death occurred in the latter patient after 23 days of hospitalization.

Complications during first month after discharge from hospital. Sudden death: There were no cases (1) of sudden death. New myocardial infarction: There were 8 (21) cases of new myocardial infarction, 2 of which were fatal. One of these infarctions occurred in a 55-year-old man who previously had had two infarcts; the final infarct had been very severe. The other fatality occurred in a 71-year-old woman.

In addition, 8 (8) patients were rehospitalized because of chest pain, in connection with which, however, a new infarct could not be diagnosed. The pain could not definitely be ascribed to cardiac origin.

Discussion

Complications occurring in our hospital during ambulation of patients with myocardial infarct were very few in the present series. Although ambulation began on an average as early as 12 days after hospitalization and lasted 8 days, there was only 1 sudden death and 2 recurrences. Ten patients developed symptoms of heart failure, which were mild and transitory in 9 patients. Since ambulation in the hospital is the most critical stage of early ambulation, the findings in the present series conform well to our previously expressed opinion that early ambulation of patients with myocardial infarction involves at least no immediate risk.

As was mentioned above, our

236 patients in 1952-1954 had relatively numerous recurrences, i.e., 21 during the first month after being discharged from the hospital, in addition to which there was 1 sudden death—a combined incidence of major complications totaling 9.3 per cent. In the present series the number of recurrences dropped to 8, or 2.5 per cent. The difference in the incidence of new infarcts is highly significant ($p < 0.01$).

The composition of the two series corresponds well, as is indicated by the foregoing data. The only noteworthy differences were that ambulation was begun, on the average, 4 days earlier in the present series than in the 1952-1954 series, and that the number of female patients was definitely larger in the latter series. The last-mentioned difference suggests that the increase in the number of myocardial infarcts has evidently been greater among men. Since both of the mentioned differences might be expected to have had an unfavorable effect on the prognosis in the recent series, the difference in the incidence of recurrences cannot be explained on this basis. It appears probable, therefore, that the lower incidence of recurrent infarcts in the new series is due chiefly to continuation of the anticoagulant therapy. Likewise, it seems evident that the relatively high incidence of recurrences during the first months after discharge from the hospital in the series of 1952-1954 was not a result of early ambulation.

Summary

A series of cases reported upon by us earlier in this Journal dealt with the effect of ambulation, which began, on the average, on the sixteenth day of hospitalization, on the results of treatment of myocardial infarction. The results were favorable except that during the first month after the patients were discharged from the hospital there was a relatively large number of recurrences of infarction (9.3 per cent). Since anticoagulant therapy was discontinued in that previous series at the time the patients were discharged from hospital, we have compared the results with a more recent series from 1957-1959 in which anticoagulant therapy was continued. The series consisted of 321 patients with myocardial infarction. During their ambulation in the hospital, which in these patients was begun, on the average, on the twelfth day of hospitalization, only 1 sudden death and 2 recurrences of infarction were reported; during the first month after the patients were discharged from the hospital there were 8 new infarctions. Thus, in the new series the number of new infarctions during the first month after discharge from the hospital dropped from 9.3 to 2.5 per cent. The difference is highly significant and is probably a result of the continuation of anticoagulant therapy.

Results from study of both series of cases clearly indicate that early ambulation is not accompanied by an increased risk to the patient with myocardial infarction.

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Correlation of degree of pulmonary hypertension with morphology of the QRS in Lead V₁ in cases with evidence of systolic overloading of the right ventricle

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In recent years attempts have been made to correlate the morphology of the tracings obtained with the right precordial electrocardiographic leads with the right ventricular pressure.[1-11] In most of these studies the two types of right ventricular overloading were not separated.[11,12,13] The present analysis was undertaken to study the correlation between the initial component of the QRS complex in Lead V_1 and the ratio of right ventricular to systemic systolic pressure in cases of systolic overloading of the right ventricle.

Material and method

The material was selected from 1,070 consecutive catheterizations of the right heart. In 227 cases there was hemodynamic and anatomic evidence of impedance to right ventricular emptying which resulted in systolic overloading of the right ventricle. We considered right ventricular hypertension to be present if right ventricular pressure was above 40 mm. Hg; however, in an attempt to exclude cases of flow hypertension, we did not include cases of ventricular septal defect and atrial septal defect unless right ventricular pressure was above 50 mm. Hg.

These cases were classified according to the ratio of the right ventricular to systemic systolic pressure. Group I—right ventricular pressure greater than systemic pressure by 15 mm. Hg or more. Group II—right ventricular pressure and systemic pressure balanced, showing a pressure difference of no more than 15 mm. Hg. Group III—systemic pressure greater than right ventricular pressure by 15 mm. Hg or more.

Most pressures were recorded simultaneously in the right ventricle and a systemic artery, but in a few cases the left ventricular pressures were recorded. It is recognized that pressures in the femoral or radial artery may be higher than pressure in the left ventricle, and this was noted at times in this series. Consequently, a spread of 15 mm. Hg was used to separate these groups.

Electrocardiograms were recorded in the standard fashion, and Lead V_1 was selected for analysis. This lead was chosen since it is universally used. It can be accurately placed by easily recognized anatomic landmarks, and usually a transitional type of complex is not recorded at this position. The tracings from each of the aforementioned groups were analyzed, first with

This [illegible] was done in the Cardiovascular Laboratory, University of Kansas Medical Center, Kansas City, Kans., [illegible] the direction of E. G. Dimond, M.D.
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regard to the diagnosis of systolic overloading of the right ventricle and second with regard to the initial component of the QRS complex in Lead V1. The criteria followed for systolic overloading of the right ventricle are those given by Cabrera[11,12]: RS, Rs, rR', R with or without initial slurring and qR complexes in the right precordial leads; in certain circumstances a small notched QRS complex may also be found. In analyzing the initial component of the QRS complex, we used the following factors: (1) the presence of a clean R wave, (2) an initially slurred R wave, or (3) a qR complex. At times a very small initial r of less than 0.2 mv. followed by an R wave was found and this was considered to be an initial slurring of the R wave. Vectorcardiograms were taken in most of the cases using the Grishman cube reference frame.

Results

Group I. In 28 cases the right ventricular pressure was greater than the systemic pressure: in 22 cases (78 per cent) there was a q wave in Lead V1, and in 6 cases (22 per cent) there was initial slurring of the upstroke of the R wave in Lead V1.

The anatomic diagnoses were: atrial septal defect with pulmonary stenosis 13 cases, pulmonary stenosis with intact septum 10 cases, mitral stenosis 2 cases, atrial septal defect with pulmonary hypertension 2 cases, primary pulmonary hypertension 1 case.

Group II. In 114 cases there were balanced right ventricular and systemic pressures: in 87 cases (77 per cent) initial slurring of the upstroke of the R wave in Lead V_1, in 16 cases (14 per cent) a clean R wave in Lead V_1, in 6 cases (5 per cent) no electrocardiographic evidence fulfilling the criteria for systolic overloading of the right ventricle.

The anatomic diagnoses were: tetralogy of Fallot 43 cases, ventricular septal defect with pulmonary hypertension 35 cases, transposition of the great vessels 5 cases, ventricular septal defect with pulmonary stenosis 5 cases, pulmonary stenosis with intact septum 5 cases, mitral stenosis 3 cases, atrial septal defect with pulmonary stenosis 3 cases, pentalogy of Fallot 2 cases, truncus arteriosus 2 cases, atrial septal defect plus ventricular septal defect plus pulmonary hypertension 2 cases, primary pulmonary hypertension 2 cases, atrioventricularis communis with pulmonary hypertension 1 case, corrected transposition 1 case, ventricular septal defect plus patent ductus arteriosus plus pulmonary hypertension 1 case, single ventricle 1 case, aortic pulmonary communication with pulmonary hypertension 1 case.

Group III. In 85 cases systemic pressure was greater than right ventricular pressure. In 63 cases (75 per cent) there was a clean R wave in Lead V1; in 9 cases (10 per cent) initial slurring of the upstroke of the R wave in Lead V_1; in 13 cases (15 per cent) no electrocardiographic evidence fulfilling the criteria for systolic overloading of the right ventricle.

The anatomic diagnoses were: ventricular septal defect with pulmonary hypertension 26 cases, mitral stenosis 20 cases, pulmonary stenosis with intact septum 14 cases, patent ductus arteriosus with pulmonary hypertension 5 cases, ventricular septal defect with pulmonary stenosis 4 cases, atrial septal defect with pulmonary hypertension 4 cases, atrioventricularis communis with pulmonary hypertension 4 cases, chronic cor pulmonale 3 cases, tetralogy of Fallot after Brock operation 1 case, aortic pulmonary communication with pulmonary hypertension 1 case, ventricular septal defect with pulmonary hypertension plus coarctation 1 case, patent ductus arteriosus with pulmonary stenosis 1 case.

Discussion

Authors frequently have stressed the poor correlation between electrocardiographic hypertrophy and anatomic hypertrophy of the heart.[13,14] More recently, closer correlation has been found when the type of work (systolic or diastolic overloading) of the heart is considered.[4] In our study a high percentage of electrocardiograms fulfilled

Table I

	Q wave	*Slurred R*	*Clean R*	*No systolic overloading*
Group I	78%	22%	—	—
Group II	5%	7%	14%	4%
Group III	—	10%	75%	15%

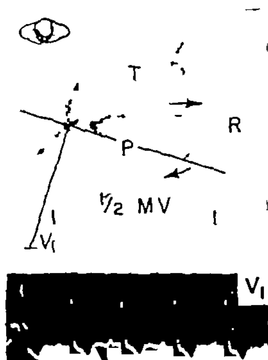


Fig 1 The R loop is seen pointing to the left situated on the negative side of the Lead V1 ... and giving q ... on this lead The T and P loops are ... visualized (horizontal plane)

the criteria for systolic overloading of the right ventricle At the same time the ratio of right ventricular to systemic pressure correlated well with the configuration of the initial component of the QRS complex in Lead V1

Table I shows that the probability of finding a q wave in Lead V1 in patients in whom the right ventricular pressure is greater than the systemic pressure (Group I) is 78 per cent (p = 0 78) In this group conditions were found that resulted in very high right ventricular pressure such as trilogy of Fallot and tight pulmonary stenosis and no case of an open ventricular septum was found These findings suggest that a ventricular septal defect with or without another defect is an unlikely diagnosis in the presence of a q wave in Lead V1 The explanation of this q wave is controversial On the basis of animal experimentation Sodi Pallares states that the right atrium is enlarged and that this dilated chamber transmits its variation in potential to the right precordial leads It is known that in the absence of myocardial infarction or complete right bundle branch block a qR complex is usually found in cases of severe systolic overloading of the right ventricle so that the presence of an enlarged right atrium is almost obligatory in these cases Myers showed that in cases of right ventricular hypertrophy qR or QR patterns were recorded in leads near the right atrioventricular groove suggesting right to left septal activation [1] This correlates well with the known anatomic finding which shows the right ventricular portion of the interventricular septum to be the predominant septal muscular mass in cases of severe right ventricular hypertrophy [17, 4] The horizontal loop of the vectorcardiogram in the cases of our Group I revealed the initial component to be deviated posteriorly and to the left even with high amplification suggesting that the predominant septal vectors are from right to left (Fig 1) If this is true we can infer that the septal activation is directly related to the thickness of the respective left or right portions of the septum

There is a probability of 77 per cent (p = 0 77) of finding initial slurring of the upstroke of the R wave in Lead V1 when

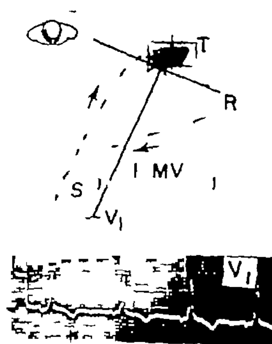


Fig ... The initial component of the QRS loop perpendicular to the Lead V1 ... giving slurring of QRS in Lead V1 (horizontal pla...

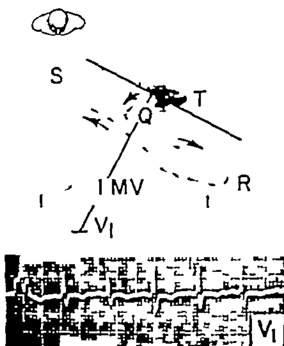


Fig. 3. Almost all of the QRS loop ... on the positive side of Lead V_1. Note the clean R wave (horizontal plane).

the right ventricular pressure is balanced with the systemic pressure (see Table I and Fig. 2). We found in Group II a high incidence of conditions with open ventricular septum. We know according to hemodynamically well-established facts that in ventricular septal defect the right ventricular pressure cannot be higher than the left ventricular pressure unless the defect is very small.[17] Tetralogy of Fallot and ventricular septal defect with pulmonary hypertension were the most common abnormalities in this group, and transposition, truncus arteriosus, and pentalogy occurred *only in this group*. In Group II only 5 per cent of the cases had a q wave in Lead V_1 (see Table I), so the probability ($p = 0.05$) of finding a q wave in Lead V_1 when the pressures in the ventricles are balanced is very small. The initial slurring of the R wave is believed to be of septal origin.[22] Sodi Pallares has recorded intracavitary electrocardiograms on the surface of the right septum in cases with initial slurring of the R wave in the right precordial leads. He found some delay in the arrival of the activation wave at the lower portions of the right septum. Because the delay correlated very well with the initial slurring of the R wave in Lead V_1 and because he considered this delay to be an indication of some degree of right bundle branch block, he concluded that the initial slurring meant a partial block. Velasco and associates[23] suggest that large right septal vectors in systolic overloading of the right ventricle neutralize the left septal vectors.

In Group III 75 per cent of the cases showed a clean R wave in Lead V_1. Since in this group the right ventricular pressure was below the left ventricular pressure or systemic pressure, there was a 75 per cent probability ($p = 0.75$) that cases with this pressure ratio would have a clean R wave in Lead V_1. The conditions more frequently found in this group were ventricular septal defect with pulmonary hypertension, mitral stenosis, and pulmonary stenosis with intact septum. In 10 per cent of the electrocardiograms in this group ($p = 0.10$) we found an initial slurring of the R wave in Lead V_1. In most of these cases the right ventricular pressure was near (within 15 mm. Hg) the level of systemic or left ventricular pressure. An RS pattern in Lead V_1 was found very frequently in this group. The clean R wave of the cases of Group III could be explained by the sum of the left septal vectors and right free ventricular wall vectors (Fig. 3). Furthermore, we believe that the ratio of right ventricular to systemic pressure is directly responsible for the septal conditions that give rise to this type of QRS-complex alteration. In 15 per cent ($p = 0.15$) of the cases in Group III we found no evidence of systolic overloading of the right ventricle, and most of these tracings showed diastolic overloading of the right ventricle. These were most frequently cases of ventricular septal defect and atrial septal defect with moderate elevation of right ventricular pressure. A qR pattern was not found in Group III. In our few cases of chronic cor pulmonale a pattern compatible with systolic overloading of the right ventricle was not found, probably because the heart is often anatomically displaced inferiorly by pulmonary emphysema.[24]

We believe that a specific electrocardiographic pattern which can be correlated with proved hemodynamic findings has considerable practical diagnostic significance

The electrocardiogram does not invariably reflect the hemodynamic changes in the heart possibly because of the sensitivity of the lead system to influences such as body shape and the electrical position of the heart It is hoped that the new corrected orthogonal lead systems will better reflect the hemodynamic conditions

Summary and conclusions

1 A study of the initial component of the QRS complex in Lead V_1 and its relationship to the right ventricular–systemic pressure ratio in cases of systolic overloading of the right ventricle is presented Three groups were studied and classified according to the right ventricular–systemic pressure ratio

2 In the group in which the right ventricular pressure was greater than the left ventricular pressure 78 per cent of the tracings had a qR complex in the group in which there were balanced pressures in the ventricles 77 per cent had an initial slurring of the upstroke of the R wave and in the group in which the left ventricular pressure was greater than the right ventricular pressure 75 per cent of the tracings had a clean R wave

3 These electrocardiographic findings are shown to be useful in the differentiation of conditions with open or closed ventricular septum

4 An explanation of the behavior of the initial component of the R wave in Lead V is attempted with emphasis on the importance of right ventricular hypertrophy

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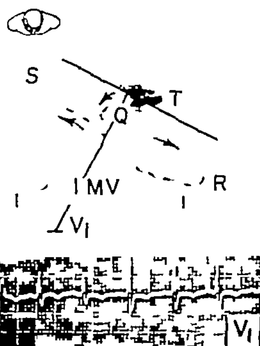


Fig 3 Almost all of the QRS loop is on the positive side of Lead V Note the clean R w (horizontal plane)

the right ventricular pressure is balanced with the systemic pressure (see Table I and Fig 2) We found in Group II a high incidence of conditions with open ventricular septum We know according to hemodynamically well-established facts that in ventricular septal defect the right ventricular pressure cannot be higher than the left ventricular pressure unless the defect is very small[27] Tetralogy of Fallot and ventricular septal defect with pulmonary hypertension were the most common abnormalities in this group and transposition truncus arteriosus and pentalogy occurred only in this group In Group II only 5 per cent of the cases had a q wave in Lead V_1 (see Table I) so the probability ($p = 0.05$) of finding a q wave in Lead V_1 when the pressures in the ventricles are balanced is very small The initial slurring of the R wave is believed to be of septal origin[8] Sodi Pallares has recorded intracavitary electrocardiograms on the surface of the right septum in cases with initial slurring of the R wave in the right precordial leads He found some delay in the arrival of the activation wave at the lower portions of the right septum Because the delay correlated very well with the initial slurring of the R wave in Lead V_1 and because he considered this delay to be an indication of some degree of right bundle branch block he concluded that the initial slurring meant a partial block[2] Velasco and associates[22] suggest that large right septal vectors in systolic overloading of the right ventricle neutralize the left septal vectors

In Group III 75 per cent of the cases showed a clean R wave in Lead V_1 Since in this group the right ventricular pressure was below the left ventricular pressure or systemic pressure there was a 75 per cent probability ($p = 0.75$) that cases with this pressure ratio would have a clean R wave in Lead V_1 The conditions more frequently found in this group were ventricular septal defect with pulmonary hypertension mitral stenosis and pulmonary stenosis with intact septum In 10 per cent of the electrocardiograms in this group ($p = 0.10$) we found an initial slurring of the R wave in Lead V In most of these cases the right ventricular pressure was near (within 15 mm Hg) the level of systemic or left ventricular pressure An RS pattern in Lead V_1 was found very frequently in this group The clean R wave of the cases of Group III could be explained by the sum of the left septal vectors and right free ventricular wall vectors (Fig 3) Furthermore we believe that the ratio of right ventricular to systemic pressure is directly responsible for the septal conditions that give rise to this type of QRS-complex alteration In 15 per cent ($p = 0.15$) of the cases in Group III we found no evidence of systolic overloading of the right ventricle and most of these tracings showed diastolic overloading of the right ventricle These were most frequently cases of ventricular septal defect and atrial septal defect with moderate elevation of right ventricular pressure A qR pattern was not found in Group III In our few cases of chronic cor pulmonale a pattern compatible with systolic overloading of the right ventricle was not found probably because the heart is often anatomically displaced inferiorly by pulmonary emphysema[1]

We believe that a specific electrocardiographic pattern which can be correlated with proved hemodynamic findings has considerable practical diagnostic significance

Right bundle branch system block in healthy young people

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Instances of right bundle branch system block (RBBSB) pattern for which no underlying cause is clinically apparent are found sporadically among young individuals and in electrocardiographic surveys of apparently healthy populations.[1-3] The significance of the electrocardiographic pattern in any particular case is usually a matter of speculation. The block pattern in such cases could reasonably be regarded as (1) a normal variant, (2) an indication of increased diastolic (input) load of the right ventricle as in uncomplicated interatrial septal defect, or (3) an isolated abnormality of intraventricular conduction. Results of right heart catheterization in such cases have rarely been reported.

This communication deals with the clinical and hemodynamic findings in 4 such individuals. The significance of the apparently isolated electrocardiographic abnormality is assessed.

Method

Each of the 4 cases was drawn from the files of the Cardiac Catheterization Unit on the basis of a clear-cut electrocardiographic pattern of RBBSB for which no underlying cause was clinically apparent. Complete right bundle branch system block was considered to be present when the QRS duration in any limb lead was 0.11 second or greater in association with a broad prominent secondary R wave (R′) in the right precordial leads. Incomplete right bundle branch system block was diagnosed when the contour was as described above but the QRS duration in any limb lead did not exceed 0.10 second. Right heart catheterization was performed as described previously.[4] In addition, the right ventricular electrical-mechanical (E-M) interval was determined in each case. This is the interval between the onset of QRS in the electrocardiogram (Lead II) and the simultaneously recorded rise in right ventricular systolic pressure. Measurement was made to the nearest 0.01 second and 0.005 second was then subtracted in order to correct for the mechanical delay in transmission of the pulse through the catheter. Normal criteria for the E-M interval were established on the basis of this measurement in 15 cases in which electrocardiographic and hemodynamic findings were normal.

Results

Clinical data pertinent to the heart are summarized in Table I. The electrocardiograms are shown in Figs. 1 and 2. The right bundle branch system block pattern

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*The term "right bundle branch system block" [illegible] the uncertainty [illegible] defect [illegible] from [illegible] wall.

Table I. Summary of clinical data

Case number	Sex	Age (yr.)	Symptom	Auscultation	Radiologic finding	Remarks
1	M	15	None	S widely split fixed M † soft widely split Grade 2* mid systolic murmur in second left intercostal space	Normal	Murmur since birth interatrial septal defect suspected
2	F	17	None	S widely split fixed M widely split Grade 2 mid systolic murmur in fourth left intercostal space	Normal	——
3	F	30	Questionable dyspnea during pregnancies only	S widely split fixed Grade 2 mid systolic murmur in second left intercostal space	Slight dilatation of ascending aorta forceful hilar pulsations	Atrial septal defect suspected
4	M	17	Questionable dyspnea during exercise at capacity	Normal	Slight transverse enlargement of heart in posteroanterior projection	Pectus excavatum trained athlete

*Second sound at the pulmonary area.
†First sound at the mitral area.
*Out of Grades 1-6

was complete in the first 3 cases and incomplete in the fourth. QRS durations and E-M intervals are listed in Table II along with control data. It can be seen that the E-M interval is definitely prolonged in each case. The usual catheterization data were within normal limits at rest in all instances according to previously delineated criteria.[1] In Cases 2 and 3 the hemodynamic responses to mild exercise were normal and in Case 4 the hemodynamic response to exercise at capacity was normal. There has been a 3 year follow-up of the first 3 cases during which time no change in clinical or electrocardiographic status was noted.

Discussion

In a recent study of 100 healthy subjects Bryant[9] found secondary R waves in certain right precordial leads in 95 per cent of the subjects who were under 40 years of age and in 22 per cent of the subjects who were beyond 40 years of age. It was postulated that these patterns reflect a *normal* order of ventricular activation and represent projection on appropriate leads of electrical potentials from the region of the outflow tract of the right ventricle usually the last part of the myocardium to be activated.[1,11] However, in the 4 cases of this report the electrocardiographic alterations were found to be more marked than those described by Bryant and co-workers[9,14,15] and others.[4] Furthermore, prolongation of the interval between onset of electrical systole and onset of right ventricular mechanical systole, a constant feature in this series (Table II), provides evidence that the electrocardiographic contour in these cases cannot be regarded as a normal variant. A significant prolongation of this interval when compared with the normal would appear to be a valid indication of abnormal delay in onset of right ventricular contraction and thus of slowed right intraventricular conduction. An *incomplete RBBSB pattern* such as that in Case 4 of this series has been reported in other instances of pectus excavatum and attributed to an unusual rotation of the heart.[17] Again, such an

explanation does not satisfy the present case in view of the prolonged E M interval

Diastolic (input) overload of the right ventricle as typified by interatrial septal defect is commonly associated with an RBBSB pattern [1, 1] usually incomplete Recent studies suggest that this pattern may not be due to actual delay in right intraventricular conduction but rather to right ventricular outflow tract *hypertrophy* which exaggerates the terminal QRS forces with or without alteration in position of the heart related to enlargement on the right side— in such cases the right ventricular E M interval is usually but not invariably normal [7, 8, 22, 23] On the other hand a RBBSB pattern does not necessarily imply the presence of right ventricular hypertrophy and the latter is notoriously difficult to recognize from the electrocardiogram in the presence of an equivocal RBBSB [4] In the present group of cases any component of hypertrophy seems to be ruled out on the basis of right heart catheterization which failed to reveal the presence of intracardiac shunts or of abnormal levels of pressure It has been stated that the electrocardiographic pattern associated with right ventricular diastolic overload may be distinguished from a conduction delay in the right bundle branch (with prolonged E M interval) vectorcardiographically or by simultaneous recording of certain scalar leads (see Schultz in Reference 25) However the former has been disputed [24] and a RBBSB pattern associated with prolongation of the E M interval is sometimes found in proved cases of interatrial septal defect [7, 23]

Table II *Relationship of* QRS *duration to electrical mechanical* (E M) *interval*

Case number	*QRS duration* (sec)	*E M interval* (sec)
1	0 14	0 105
2	0 14	0 135
3	0 12	0 095
4	0 09	0 095
Controls (15 cases)	Range 0 06–0 08	Range 0 055–0 075

This study is in keeping with a previous one of Braunwald and associates in demonstrating that the fully developed pattern of RBBSB in young people without evidence of associated heart disease indeed reflects a defect in intraventricular conduction However it sheds no light directly on the etiology or pathogenesis of the conduction disturbance It is not known whether the conduction disturbance dates from birth nor is it known whether there is actual anatomic involvement of the right bundle branch Recent suitably detailed correlative studies of *seriously diseased* hearts indicate that complete RBBSB is almost always associated with an organic lesion of the right bundle branch [27, 1] whereas incomplete RBBSB is commonly associated with right ventricular hypertrophy and in only about one quarter of the cases with definite involvement of the right bundle branch [27]

Because this electrocardiographic pattern is associated with interruption of the right bundle branch experimentally and with known heart disease clinically the tendency has been to assume that an organic lesion is in all probability at the root of all such disturbances in conduction [29, 30] Moreover it has been suggested that because of the very nature of its morphology [31] the right bundle branch is more likely to be affected by localized otherwise benign organic processes than is the left bundle branch [30] and isolated left bundle branch system block in young individuals is indeed relatively rare However on the assumption that the conduction defect reflects organic involvement of the right bundle branch consideration of reasonable etiological possibilities does not bring to mind any single one likely to satisfy the present and similar cases The conduction defect in such cases has been attributed for example to a *congenital* deformity of the right bundle branch system [1, 3] but such actual deformity has been described only rarely and then in association with severe heart disease [27] Although *arteriosclerotic coronary artery disease* is certainly a most common cause of RBBSB and pathol... evidence of coronary artery invol... has been found not infrequentl... tively young males it appears ... at it could be consistently th...

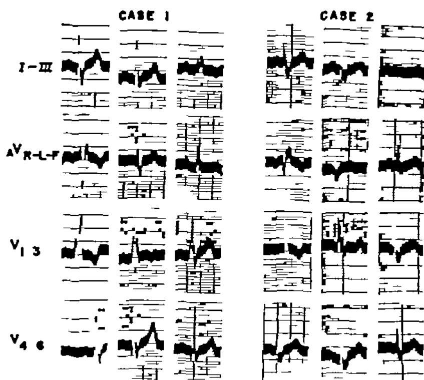


Fig. 1. Electrocardiograms of Cases 1 and 2. See text.

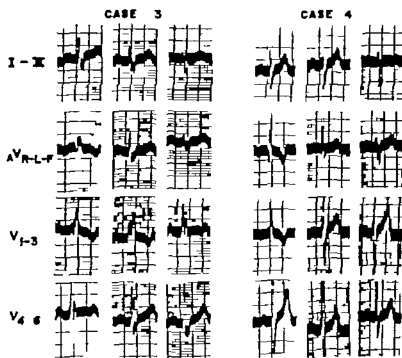


Fig. 2. Electrocardiograms of Cases 3 and 4. See text.

the electrocardiographic findings in this group (in which 2 of the subjects were females and 3 were under 18 years of age). Such defects in conduction have been attributed to an otherwise benign or clinically inapparent *myocarditis*.[1] This hypothesis is attractive. The clinical incidence of myocarditis is observed to be less than the pathologic,[14] for the diagnosis is easily missed in life. However, RBBSB is a rather uncommon feature of known myocarditis,[14,15] and when present in instances of nonspecific (viral) myocarditis it usually appears to be associated with the clinically and pathologically more severe or chronic cases,[16] or to be accompanied on late follow-up by other stigmata of heart disease.[17] Cases of known myocarditis manifested at some stage by RBBSB alone might link this etiology with the present cases, but except for certain instances of chronic Chagas' disease, no such documentation could be found. There was no history of acute rheumatic fever in the present cases, and in none were there characteristic murmurs that might implicate *rheumatic heart disease*.

Although the conduction defect in these cases could perhaps have a basis of multiple etiologies, the difficulty of establishing any particular one raises the question: Need there be an organic basis? It should be stressed that the finding of an electrocardiographic pattern of right bundle branch block similar to that produced experimentally does not prove the presence of a corresponding bundle branch lesion in man. Actually, the electrocardiogram does *not* differentiate among three possibilities: (1) complete (anatomic) interruption of conduction in a main bundle branch, (2) anatomic interruption of conduction in a parietal portion of the conduction system, and (3) mere *slowing* of conduction in some part of a main bundle branch so that activation of the right ventricle is effected via transseptal impulse conduction from the left.[1] Simple prolongation of the relative refractory period somewhere along the conduction system in relation to the usual heart rate could have such an effect, and instances of intermittent, at times rate-dependent, RBBSB are not uncommon in young healthy individuals as well as in older individuals with or without associated heart disease.[1,4,6,11,18] With particular regard to the last of these three possible mechanisms, the line between involvement by disease and physiologic variation becomes thin indeed, and it remains to be proved that the disturbance in conduction, although giving rise to an abnormal electrocardiogram, is in any way the result of a disease process. It has been suggested in the past that RBBSB may at times be physiologic,[11] or in cases such as the present ones may have a physicochemical rather than an organic basis.

As long ago as 1925[4] it was recognized that an electrocardiographic pattern of RBBSB does not of itself imply a poor prognosis. Subsequent studies,[1,4,8] including cases followed up for almost 30 years, have tended to fortify this point of view, and it is now accepted that the prognosis of a patient with a RBBSB pattern is determined by the underlying heart disease.[11,14,8] Thus it appears unjustified at present to attach the stigma of heart disease, however benign, to cases such as those in the present study in which RBBSB is present but is unassociated with clinical or laboratory evidence of cardiac pathology.

Summary

The electrocardiographic pattern of right bundle branch system block was an isolated finding in a group of 4 young individuals who were apparently normal on the basis of clinical and hemodynamic evaluation. Prolongation of the right ventricular electrical mechanical interval provided evidence that the electrocardiographic abnormality was attributable to a conduction defect in the right side rather than to right ventricular hypertrophy or to a physiologic variant of contour. The significance of the electrocardiographic abnormality in such cases is discussed. It is concluded that the finding of an isolated right bundle branch system block in a young and apparently healthy individual cannot of itself be taken to indicate prima facie evidence of organic heart disease.

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Experimental and laboratory reports

The production of lactic acid during exercise in normal subjects and in patients with rheumatic heart disease

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It has been shown that the concentration of lactic acid in the blood (capillary, arterial, or superficial venous) of patients with heart disease is greater than that in normal subjects during a similar degree of exercise.[1-4] Weiss and Ellis also demonstrated that the oxygen content was lower and the concentration of lactic acid higher in the femoral venous blood of patients with heart disease than in that of normal subjects immediately after similar leg exercise. Many patients with heart disease are unable to increase the cardiac output to a normal degree during exercise.[7] Despite a remarkable reduction of blood flow through certain regional circulations (splanchnic, renal, nonexercising muscle, and skin[8]) the blood flow through the exercising limbs is less than that in normal subjects under the same conditions. Since almost all of the increased oxygen uptake is in the exercising muscles, the oxygen content of the blood returning from the exercising limbs is considerably less than that in normal subjects during similar exercise.[9] Therefore, the oxygen tensions in the exercising muscles must be lower than those in normal subjects. It has been assumed that the increased production of lactic acid in such patients during exercise is due to the influence of lowered oxygen tensions on the metabolism of exercising muscle. The reduction of blood flow through the liver and kidney may, however, also delay the catabolism and excretion of lactic acid during exercise. Furthermore, the marked reduction of blood flow through many other tissues not involved in the exercise may reduce the amount of lactic acid diffusing into or even being catabolized by these tissues.

The purpose of the present study has been to investigate more precisely the relationship between the hemodynamic response to exercise and the production of lactic acid in normal subjects and in patients with heart disease of varying severity. Direct measurements of the concentration of lactic acid and oxygen in the arterial blood and venous blood leaving the exercising legs have been carried out in an attempt to discover a more precise relationship between the rate of production of lactic acid in exercising muscle, the

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Table I Details concerning normal subjects and patients studied

Subject number	Sex	Age (yr)	Weight (Kg)	BSA (M²)	Diagnosis
					Group A
A807	F	50	68 2	1 72	Normal
A82	F	36	55 5	1 54	Normal
A832	F	37	59 1	1 57	Normal
A812	F	59	58 6	1 58	Primary pulmonary hypertension
A874	F	36	55 9	1 55	Mitral stenosis Aortic stenosis and incompetence (F)
A878	F	28	56 4	1 60	Mitral stenosis and incompetence (F)
A834	F	39	80 5	2 05	Mitral stenosis and incompetence (F)
A836	F	46	6 7	1 64	Mitral stenosis (F)
A840	M	42	50 9	1 61	Mitral stenosis (F)
A842	F	35	59 1	1 59	Mitral stenosis
A850	F	38	54 1	1 50	Mitral stenosis (F)
A854	F	50	52 3	1 53	Mitral stenosis and incompetence Aortic stenosis (F)
A857	F	18	52 7	1 54	Mitral stenosis and aortic incompetence
A865	F	37	56 4	1 56	Mitral stenosis
A875	M	45	61 8	1 68	Mitral stenosis (F)
					Group B
A774	F	24	61 4	1 62	Normal
A780	F	25	39 1	1 35	Mitral stenosis
A785	F	33	41 8	1 32	Mitral stenosis
A787	F	54	51 6	1 54	Mitral stenosis Systemic hypertension (F)
A791	M	37	50 0	1 57	Mitral stenosis Aortic incompetence Tricuspid stenosis (F)
					Group C
A810	M	46	60 9	1 71	Normal
A833	M	44	52 7	1 60	Normal
					Group D
A970	F	41	52 3	1 62	Normal
A795	F	36	40 9	1 32	Mitral stenosis and aortic incompetence (F)
A801	F	44	68 2	1 74	Mitral stenosis and incompetence (F)
A803	M	45	73 2	1 91	Mitral stenosis (F)
A871	M	38	74 5	1 91	Mitral stenosis and aortic incompetence (F)
A91	F	55	62 7	1 71	Myocarditis
A927	F	45	66 8	1 84	Mitral stenosis (F)
A929	F	35	44 5	1 39	Mitral stenosis Aortic stenosis and incompetence
A934	F	28	50 9	1 49	Mitral stenosis and aortic incompetence

(F) Auricular fibrillation

oxygen uptake and the levels of oxygenation of the blood returning from the exercising leg. The validity of the assumption that the concentration of lactic acid in blood collected from the nonexercising areas is proportional to the rate of production of lactic acid in the exercising muscles during a relatively steady state has also been investigated

The concentration of lactic acid in arterial blood during rest was also measured in 41 patients confined to bed. Seventeen of these patients had normal heart and lungs and the other 24 had

Table II The effect of exercise on the levels of lactic acid in the arterial and femoral venous blood of Groups A B and C

Subject number	Group	BA or FV	Rest		Exercise 6 min	Exercise 8 min	Exercise 10 min	Mean	Recovery	Fem VAL / Fem AVO₂ (exercise) (mg lactic acid/ml O_2)	R_{O_2} (exercise)	M_L (exercise) (mg/min)
							Normal Subjects					
A807	A	FV	9 6	—	11 8	12 0	11 8	11 9	14 2	+0 10	01	17
		BA	9 2	—	10 6	11 0	12 0	11 2	12 2			
A822	A	FV	15 0	15 2	33 0	32 4	31 4	32 2	18 6			
		BA	13 2	12 8	27 8	27 4	27 4	27 5	16 4	+0 41	05	244
A832	A	FV	9 7	10 0	37 2	43 2	39 4	40 0	21 8			
		BA	10 1	10 4	32 8	38 0	38 0	36 3	20 0	+0 34	04	260
A774	B	FV	13 8	—	30 6	30 2	31 4	30 8	—			
		BA	11 8	—	23 6	26 0	27 4	25 7	—	+0 49	06	290
A774	B	FV	7 0	—	46 8	46 8	45 8	46 5	—			
		BA	6 8	—	36 8	38 4	40 0	38 4	—	+0 70	09	6 5
A810	C	FV	9 2	—	13 4	13 0	12 2	12 9	10 6			
		BA	8 6	—	12 8	12 2	11 2	12 1	9 6	+0 07	01	32
A833	C	FV	9 2	9 6	75 6	70 8	70 8	77 4	35 0			
		BA	8 0	9 2	61 8	68 4	66 0	65 4	28 6	+0 42	05	453

VAL = Venoarterial difference of lactic acid concentration (mg/100 ml)
AVO₂ = Arteriovenous difference of oxygen content (ml/100 ml)
R_{O_2} = Venoarterial difference of lactic acid (mM/L) × 0 5 / Arteriovenous difference of oxygen (mM/L)
BA = Brachial arterial blood FV = Femoral venous blood
M_L = Estimated blood flow leg during exercise (L/min) × VAL (mg/100 ml) × 10 = rate of liberation of lactic acid into femoral blood (mg/min)

heart disease Thirteen of these patients with heart disease had shortness of breath on slight or moderate exertion (Grade III according to the New York Heart Association classification) and the other 11 were in frank clinical congestive heart failure as evidenced by an abnormally raised systemic venous pressure with or without edema (Grade IV)

Methods

The estimation of lactic acid in blood has been carried out on 5 ml samples using the method of Barker and Summerson[10] as modified by Mitchell and Cournand[11] the blood was hemolyzed in water immediately after collection In this laboratory the mean and standard deviation of the difference of 43 pairs of blood samples taken 2 minutes apart from the same blood vessel during rest were 0 38 and 0 315 mg/100 ml respectively the average of all readings was 10 28 mg/100 ml

Preliminary studies of the effect of exercise in normal subjects and in patients with heart disease showed that the concentration of lactic acid in arterial blood rose rapidly during the first few minutes and then achieved a steady level by about the fifth minute It was found that if exercise was continued beyond this time however the concentration of lactic acid usually diminished again after about the tenth to fifteenth minute of exercise although the rate of external work and the oxygen uptake remained unchanged This phenomenon was originally described in normal subjects by Bang[12] Since the length of exercise that can be undertaken by patients with heart disease is limited a period of 10 minutes of exercise was chosen and the levels of lactic acid in the brachial

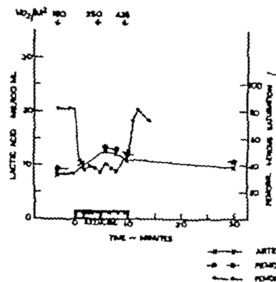
arterial and femoral venous blood were measured during the second half of this period It was hoped that at this time a reasonably steady level of lactic acid in the blood would be maintained between the initial rise and subsequent decline and evidence will be presented that this was so

The effects of exercise were studied in 7 healthy subjects and in 24 patients with heart disease Details of the normal subjects and of the patients are given in Table I It will be noted that all except 2 of the patients had rheumatic heart disease Of the two exceptions one had pulmonary hypertension of unknown etiology and the other had developed recurrent heart failure without any demonstrable valvular or congenital heart disease pulmonary or systemic hypertension or evidence of coronary disease There was no evidence of peripheral vascular disease or

Table II The effect of exercise on the levels of lactic acid in the arterial and femoral venous blood of Groups A B and C— Cont d

Subject number	Group	BA or FV	Rest	Rest	Lactic acid (mg /100 ml of blood) Exercise 6 min	8 min	10 min	Max	Recovery	F m A: Fem A-V O2 (exercise) (mg lactic acid/ml O2)	RQ (exercise)	M (exercise) (mg /ml)
					Cardiac Patients							
A812	A	FV	11 8	—	36 0	32 4	32 0	33 5	15 0			
		BA	10 4	—	28 8	28 2	28 2	28 4	13 0	+0 8	03	81
A824	A	FV	8 7	8 8	23 4	23 2	22 6	23 1	12 9			
		BA	2	7 6	17 8	17 9	18 2	18 0	9 8	+0 41	05	94
A828	A	FV	8 3	9 2	39 2	3 2	36 0	37 5	20 1			
		BA	7 7	8 4	34 4	32 2	32 4	33 0	16 4	+0 40	05	244
A834	A	FV	11 5	11 9	14 4	14 4	15 0	14 6	15 4			
		BA	10 0	10 1	13 1	13 2	13 4	13 2	12 7	+0 08	01	16
A836	A	FV	11 4	10 8	105 8	116 4	111 6	111 3	71 4			
		BA	9 6	—	92 4	97 2	94 8	94 8	6 2	+0 8	10	615
A840	A	FV	10 4	10 5	30 8	32 5	33 2	32 2	10 8			
		BA	9 2	8 4	25 6	25 9	26 1	25 9	13 6	+0 38	05	180
A842	A	FV	10 2	10 0	33 7	34 4	33 2	33 8	16 7			
		BA	9 3	10 4	28 8	30 2	30 1	29 7	13 6	+0 34	01	264
A850	A	FV	14 0	14 0	37 0	40 8	46 0	41	20 5			
		BA	11 9	12 1	25 6	31 8	34	30 5	15 3	+0 62	08	100
A854	A	FV	8 8	8 6	32 0	29 8	28 6	30 2	1 5			
		BA	7 2	7 3	24 8	3 4	24 4	4 9	—	+0 33	04	158
A857	A	FV	9 1	9 1	69 4	80 0	80 4	76 6	38 8			
		BA	8 4	7 8	66 8	65 8	66 2	66 3	33 5	+0 74	09	716
A865	A	FV	9 4	9 3	50 8	51 4	46 2	49 4	22 8			
		BA	7 8	8 0	41 0	43 0	41 8	41 9	18 9	+0 57	07	420
A875	A	FV	10 4	10 6	97 8	103 8	107 4	103 0	0 4			
		BA	8 5	8 7	85 5	96 9	95 7	9 7	0 4	+0 51	06	852
A 80	B	FV	11 2	—	42 4	44 0	44 2	43 5	21 6			
		BA	9 8	—	27 6	29 2	32 0	29 6	16 6	+0 85	11	117
A 85	B	FV	13 0	3 0	31 6	2	8 0	29 6	15 0			
		BA	1 0	11 8	28 0	27 2	24 4	6 5	—	+0 26	03	93
A797	B	FV	18 5	19 2	4 0	23 8	25 2	24 4	17 4			
		BA	20 0	20 4	23 0	23 8	25 4	24 1	20 0	+0 03	< 01	5
A791	B	FV	12 0	1 6	40 0	47 2	49 6	45 6	25 0			
		BA	10 8	10 0	34 0	40 2	46 8	40 3	2 0	+0 43	05	185

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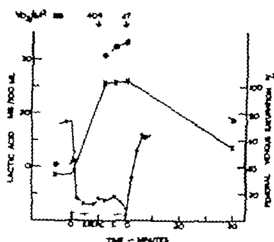


Fig. 1. The effect of leg exercise on the concentration of lactic acid in arterial and femoral venous blood and on the femoral venous blood oxygen saturation in a normal subject and in a patient with mitral stenosis at similar levels of exercise.

embolization in any of the patients studied either in the history or on physical examination. The studies were carried out in the early afternoon. All the subjects had been confined to bed without food since breakfast and had lain on the catheterization table for at least 1 hour before exercise was begun. Sodium Amytal 0.2 Gm. had

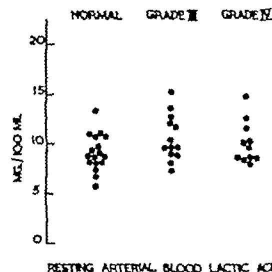


Fig. 2. The concentration of lactic acid in the arterial blood of patients resting in bed. Three groups are compared: those with normal hearts and lungs and those with Grade III and Grade IV cardiac disability (New York Heart Association classification).

been given 3 to 4 hours before the time of exercise. The exercise consisted of pedaling a bicycle ergometer for a period of 10 minutes in the recumbent position, the external work being maintained at a constant level. All subjects had practiced the procedure the day before so as to increase confidence and to determine the rate of work possible without undue stress.

The brachial artery was cannulated in all subjects. In 3 normal subjects and 12 patients (Group A), a cardiac catheter was placed with its tip in the pulmonary artery, and a length of polythene tubing was inserted directly through a needle into the femoral vein. While these patients exercised, samples of blood were taken every minute from the femoral vein, every other minute from the brachial artery, and from the pulmonary artery at the times of collection of expired gas. The oxygen saturation of these samples was measured by a spectrophotometric method.[3] Arterial blood oxygen capacities were measured spectrometrically at rest and at the seventh minute of exercise. Routine checks of the spectrophotometric technique against the Van Slyke method and against standard reed (iron content) blood capacities were also carried out. Expired air was collected into a Tissot spirometer for a period of 3

minutes at rest just prior to the exercise and during the fifth and tenth minutes of exercise Samples of expired air were analyzed in a micro Scholander apparatus Therefore the cardiac output at rest and at the fourth to fifth and ninth to tenth minutes of exercise could be estimated by the direct Fick method The degree of response of the cardiac output to exercise has been graded by use of the criteria of Donald Bishop and Wade In Grade I the response of cardiac output to exercise is only slightly impaired in Grade III the cardiac output changes little or not at all in response to exercise

In 1 normal subject studied twice and in 4 patients (Group B) the femoral vein was entered retrogradely by means of a cardiac catheter introduced into the arm In these studies the cardiac output and its response to the same level of external work was measured 20 minutes after the initial experiment by moving the tip of the cardiac catheter to the pulmonary artery

In 2 of the normal subjects (Group C) cardiac catheterization was not carried out and the response of the cardiac output to exercise was assumed to be normal In these subjects the samples of blood were drawn only from the femoral vein and brachial artery

Group D consisted of 1 normal subject and 8 cardiac patients in whom femoral venous samples were not taken These patients had the tip of the cardiac catheter in the pulmonary artery and a needle in the brachial artery The period of exercise measurement of cardiac output and measurement of lactic acid in the arterial blood followed the same protocol as that in Groups A and B

In all of the exercise studies the levels of lactic acid in the femoral venous and brachial arterial blood were measured at rest (usually twice) and then at the sixth eighth and tenth minutes of exercise In most studies these levels were also measured 20 minutes after exercise

Results

The concentration of lactic acid in the brachial arterial and femoral venous blood at rest during exercise and on recovery (20 minutes after exercise) are shown in Table II (Groups A B and C) and Table III detail the concentration of lactic acid in the brachial arterial blood under the same conditions in Group D in which group of subjects no samples of femoral venous blood were collected

The oxygen uptake ventilation respiratory quotient arterio mixed venous blood

Table III *Lactic-acid concentration in arterial blood during rest and exercise in Group D*

Case number	Arterial blood lactic acid (mg /100 ml)						
	Rest		Exercise				Recovery
			6 min	8 min	10 min	Mean	
			Normal Subject				
A970	9 4	9 3	21 8	24 6	26	24 3	14 3
			Cardiac Patients				
A79	8 6	—	14 2	14 8	15	14 7	11 4
A801	8 0	—	11 4	12 2	12 4	12 0	9 4
A803	11 4	—	58 8	60 4	61 6	60 3	26 0
A821	9 8	—	14 6	13 8	13 8	14 1	11 4
A917	12 0	11 9	48 8	58 4	55 2	54 1	29 6
A927	7 9	8 1	27 6	28 2	28 2	28 0	13 4
A929	7 4		55 5	61 1	61 2	59 3	18 0
A934	6 7	6 6	6 7	66 1	67 6	65 3	25 6

oxygen content difference and cardiac output at rest and during exercise are shown in Table IV The degree of response of the cardiac output to exercise[11] is also given The high resting cardiac output of 4 of the 5 normal subjects in whom it was measured is worthy of comment It may be recalled that similar raised values of the resting cardiac output were found in a previous study of normal healthy subjects in this laboratory [14] These normal subjects are always medical men or women who are cognizant of the risks slight though they may be of the procedure It has been shown however that in such subjects the exercising cardiac outputs are entirely

Table IV Respiratory and hemodynamic data during rest and exercise

Case number	Group	Rest					4 5 minutes	
		V	V_{O_2}/M	R_E	$\overline{AV}_{O_2}$	Q/M	V	V_{O_2}/M
								Normal
A80	A	7 54	165	0 77	4 7	3 5	15 48	240
A827	A	4 40	134	0 71	2 5	5 3	15 57	547
A832	A	4 79	138	0 75	2 4	5 8	20 09	617
A7 4	B	6 98	179	0 71	3 6	4 9	20 82	557
A 74	B	6 89	1 9	0 77	—	—	28 84	746
A810	C	9 31	150	1 02	—	—	13 69	380
A833	C	8 98	154	1 12	—	—	23 06	806
A920	D	5 01	150	0 65	3 0	5 0	13 78	463
Average		6 74	156	0 81			18 92	545
								Cardiac
A812	A	6 21	127	0 79	8 1	1 6	13 36	284
A824	A	68	142	0 73	5 9	2 4	9 89	273
A878	A	6 32	158	0 81	4 7	3 4	21 99	528
A834	*A*	*7 78*	*108*	*0 71*	*8 2*	*1 3*	*13 20*	*187*
A836	A	6 4	114	0 83	6 8	1 7	28 81	525
A840	A	8 27	158	0 6	6 1	2 6	17 98	409
A842	A	6 89	1 3	0 87	4 9	3 1	16 59	573
A850	A	6 98	167	0 81	12 9	1 3	9 68	233
A854	A	5 01	132	0 88	6 1	2 2	13 44	444
A857	A	6 36	166	0 76	3	4 7	37 07	758
A865	A	5 41	149	0 78	4 2	3 6	24 11	592
A87	A	7 12	147	0 74	4 9	3 0	52 25	1 191
A 80	B	10 50	194	0 82	12 2	1 4	16 88	253
A785	B	5 34	142	0 85	4 1	3 5	18 4	566
A 87	B	9 95	15	0 83	6 5	2 4	13 26	280
A791	B	4 52	176	0 74	6 8	1 9	16 37	383
A 95	D	5 29	141	0 70	7 6	1 9	8 07	227
A801	D	5 54	147	0 82	4 6	3 2	9 23	291
A803	D	7 41	131	0 86	4 4	3 0	30 97	553
A8 1	D	8 81	184	0 4	8 4	2 2	15 91	28
A917	D	6 40	154	0 78	4 8	3 2	9 93	377
A9 7	D	4 84	128	0 72	3 6	3 5	16 22	40
A979	D	6 06	153	0 74	5 4	2 8	34 88	519
A934	D	4 27	1 2	0 74	3 9	3 9	14 22	633
Average		6 5	147	0 78	6 2	2 7	19 07	448

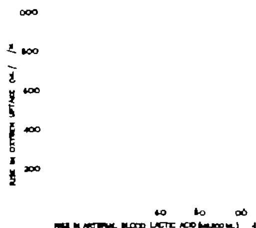
V = Liters of gas expired per minute (B T P.S.) ... and mixed venous blood (ml./100 ml.) R_E = Respiratory exchange ratio $\dot{Q}$ = Cardiac output (L./min)

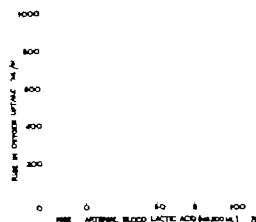
comparable to those found in studies of other normal subjects who have less expert knowledge of the procedure In the experience of this laboratory psychological stress does not cause a hyperkinetic state during exercise It is also to be noted that the only assumption made concerning the 2 healthy subjects whose right hearts were not catheterized was that the response of the cardiac output to exercise was normal in degree

The mean oxygen uptake during exercise was 533 ml /min /M [2] (rise of 377 ml /M) in the normal subjects and 452 ml /min /M (rise of 306 ml /M) in the patients with heart disease

... of exercise			9 10 minutes of exercise					$\dot{Q}$ response to exercise
R_E	$\overline{AV}_{O_2}$	$\dot{Q}/M$	V	V_{O_2}/M	R	$\overline{AV}_{O_2}$	$\dot{Q}/M$	
Subjects								
0 97	5 6	4 3	25 08	219	1 17	4 8	4 5	Normal
0 76	7 6	7 2	15 29	464	0 82	7 3	6 4	Normal
0 91	9 0	6 9	21 38	622	0 89	9 0	6 9	Normal
0 87	—	—	19 81	512	0 88	—	—	Normal
0 83	—	—	28 14	639	0 89	—	—	Normal
0 86	—	—	15 64	428	0 88	—	—	—
0 95	—	—	23 03	808	0 92	—	—	—
0 84	6 6	6 8	16 59	475	0 91	6 8	7 0	Normal
0 88			20 6	521	0 91			
Patients								
0 87	16 5	1 7	14 76	301	0 89	15 6	1 9	III
0 6	10 0	2 7	10 57	265	0 78	10 1	2 6	III
0 94	10 6	5 0	23 80	533	0 93	10 6	5 0	I
0 60	12 4	1 5	13 01	182	0 66	13 3	1 4	III
1 11	18 3	2 9	33 96	579	1 04	18 0	3 2	III
0 89	13 6	3 0	19 54	447	0 85	12 6	3 6	III
0 79	9	5 9	16 59	679	0 67	9 9	6 9	Normal
0 87	15 0	1 6	10 39	244	0 91	14 8	1 7	III
0 83	14 0	3 2	13 30	407	0 88	13 6	3 0	III
1 09	11 9	6 4	38 71	807	0 96	11 8	6 8	I
0 97	11 2	5 3	24 95	598	0 93	11 1	5 4	I
0 89	1 9	6 7	63 84	1 060	1 07	18 8	5 6	II
0 92	—	—	19 72	273	0 94	—	—	III
1 00	—	—	16 1	50?	0 94	—	—	I
0 73	—	—	12 97	260	0 80	—	—	II
1 04	—	—	18 00	382	1 03	—	—	II
0 75	10 1	2 3	8 49	225	0 78	10 0	2 2	III
0 74	8 6	3 4	11 19	328	0 78	8 7	3 8	II
1 09	11 4	4 9	31 52	543	0 99	11 5	4 7	I
0 81	13 2	2 1	13 52	254	0 78	12 8	2 0	III
1 02	13 1	2 9	10 42	430	0 93	11 9	3 6	III
0 8	10 6	3 8	17 90	439	0 87	11 0	4 0	II
0 96	14 7	3 5	35 72	334	0 97	14 8	3 6	III
1 02	11 5	5 5	16 72	707	1 01	12 1	5 9	I
0 90			20 68	457	0 89			

[illegible] taken up by the ... per minute (S.T.P.D.) $\overline{AV}_{O_2}$ = Diff [illegible] oxygen content between [illegible]





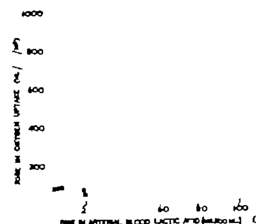


Fig 3 The relationship of the increase in the concentration of lactic acid in arterial blood to the increase in oxygen uptake during exercise *A* ● = Normal subjects O = Cardiac patient with normal cardiac-output response *B* ▲ = Patients with light and moderate impairment of cardiac response (Grades I and II Donald et al) *C* ■ = Patients with severe impairment of cardiac-output response (Grade III Donald et al [14])

The results of two representative exercise studies in a normal subject and in a patient with mitral stenosis are illustrated in Fig 1 The rise in oxygen uptake was very similar in the two studies The rise in the concentration of lactic acid was however far greater in the patient with mitral stenosis both in the arterial and femoral venous blood whereas the femoral venous–arterial lactic acid difference was also greater At the same time the femoral venous blood oxygen saturation fell to a lower level in the patient with heart disease than in the normal subject

The oxygen saturations of the brachial arterial femoral venous and pulmonary arterial blood at rest and during exercise are detailed in Table V The blood flow through the exercising legs as estimated by the method of Donald Wormald Taylor and Bishop is also given in this table

The concentrations of lactic acid in the arterial blood of patients confined to bed are shown in Fig 2 Those patients with normal hearts and lungs had a mean value of 9 17 mg /100 ml (S D = 1 77 mg /100 ml) Those with shortness of breath on mild or moderate exercise had a mean value of 10 62 mg /100 ml (S D = 2 25 mg /100 ml) Those in congestive failure had a mean value of 10 14 mg /100 ml (S D = 2 04 mg /100 ml) Although the average value for the patients with heart disease was slightly higher than that for those without heart disease the difference could readily have arisen by chance (t = 1 880 0 1 > p > 0 05) Furthermore the mean value for those in classification Grade IV was slightly less than that for those in Grade III

Discussion

Steadiness of state It is evident from the work of Bang[1] that the level of lactic acid in the blood during exercise rises steeply at first but later declines again even though the rate of external work remains unchanged Our own preliminary studies in normal subjects showed that a new constant level of lactic acid in the blood may eventually be reached if exercise is continued for long periods but that this may take more than 30 minutes to attain even with moderate degrees of activity

It is certain therefore that no ultimate steady state level of lactic acid in the blood can be reached within the space of 10 minutes of exercise Thus any measurements of lactic acid in the blood taken within this period must be related to the time of sampling as well as to metabolic activity To a certain extent therefore the times of all such measurements must be arbitrarily chosen However as previously stated our preliminary studies suggested that the maximal level of lactic acidemia usually occurred between the fifth and tenth minutes of exercise in both normal subjects and cardiac patients and that during this period a relatively steady level of lactic acid could be expected in the arterial blood It was for this reason

Table V The arterial mixed venous and femoral venous blood saturation at rest and during exercise Calculated leg blood flow during exercise

Case number	Group	Sa O₂ Rest	Sa O₂ Ex	Sv O₂ Rest	Sv O₂ Ex	Sfv O₂ Rest	Sfv O₂ Ex	F m A V O₂ Rest	F m A V O₂ Ex	Q leg exercise
					Normal Subjects					
A807	A	99	100	68	64	51	49	7 1	4	2 5
A822	A	97	97	84	58	87	37	2 0	11 4	5 2
A832	A	100	100	85	40	90	33	1 6	11 0	7 0
A774	B	97	97	74	—	9	35	8	10 5	5 7
A774	B	97	97	4	—	85	29	1 5	11 5	7 7
A810	C	99	100	—	—	82	4	3 3	11 5	4 0
A833	C	99	97	—	—	82	20	3 6	16 7	6 5
A920	D	97	98	81	63	—	—	—	—	—
					Cardiac Patients					
A812	A	96	97	60	27	68	12	6 3	18 5	1 6
A874	A	96	97	61	38	59	23	6 1	12 4	1 8
A878	A	97	97	66	30	80	25		11 3	5 4
A834	A	96	97	59	40	48	16	10 5	18 3	1
A836	A	9	95	59	10	58	0	7 0	20 2	3 7
A840	A	97	93	67	31	75	15	4	16 4	2 9
A842	A	98	96	71	44	82	31	2 9	12 0	6 5
A850	A	90	88	30	19	40	9	10 6	17	0 9
A854	A	99	98	70	34	76	4	4 7	15 9	3 0
A857	A	99	98	77	31	88	18	1 7	13 9	7 0
A865	A	96	95	73	35	68	3	5 1	13 1	5 6
A87	A	99	98	76	20	7	11	4	20 4	8 3
A780	B	98	93	31	—	54	7	8 0	15 8	0 8
A785	B	98	98	73	—	74	29	4 1	1 1	3 0
A787	B	87	81	59	—	65	9	4 7	11 4	1 8
A 91	B	99	100	61	—	7	29	4 3	12 2	3 5
A 95	D	97	97	52	34	—	—	—	—	—
A801	D	98	9	70	43	—	—	—	—	—
A803	D	96	93	75	37	—	—	—	—	—
A8 1	D	97	97	55	33	—	—	—	—	—
A917	D	9	9	69	29	—	—	—	—	—
A977	D	99	99	7	43	—	—	—	—	—
A979	D	98	98	68	2	—	—	—	—	—
A934	D	98	97	6	34	—	—	—	—	—

Sa O₂ = Arterial oxygen saturation (%) Sfv O₂ = Femoral venous oxygen saturation (%) Sv O₂ = Mixed venous oxygen saturation (%)
Q l = Estimated blood flow (l) (L/min)

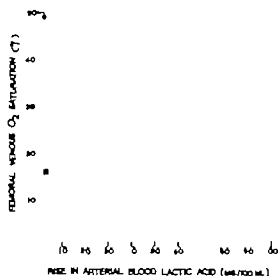


Fig. 4. The relationship of the mean femoral venous blood oxygen saturation to the mean rise in lactic acid concentration in arterial blood during the fifth to tenth minutes of exercise. Symbols as in Fig. 3.

that measurements of lactic acid during exercise were made at the sixth, eighth, and tenth minutes.

In fact, the average values of lactic acid concentration in brachial arterial blood in all subjects studied were 34.9 mg./100 ml. at 6 minutes, 37.2 mg./100 ml. at 8 minutes, and 36.8 mg./100 ml. at 10 minutes. The femoral venous samples in Groups A, B, and C had average values of 41.6, 43.9, and 42.7 mg./100 ml. at 6, 8, and 10 minutes, respectively. Thus the expectation of a reasonably steady level of concentration of lactic acid in the blood over the second half of the 10 minute period of exercise appears to have been largely justified. Measurements of oxygen uptake made at the beginning and end of this period provide a useful check on the constancy of the level of exercise at this time. The average values for all subjects were 473 ml./min./M.² at 4 to 5 minutes and again 473 ml./min./M.² at 9 to 10 minutes.

Total oxygen uptake and lactic acid. The relationship between the rise in the concentration of lactic acid in arterial blood and the rise in total body oxygen uptake during exercise is plotted in Fig. 3. Note that the oxygen uptake is standardized for body size since the level of lactic acid in the arterial blood will also be affected by body size. In the case of the normal subjects and the patient with a normal cardiac output response the relationship between these values appears to be curvilinear, particularly since it must pass through the point of origin (Fig. 3 *A*). The concentration of lactic acid in the arterial blood increases but little with slight exercise and then more abruptly as the exercise becomes heavier. The patients with heart disease differ from the normal subjects in that, with only a few exceptions, there is a greater increase in the concentration of lactic acid in arterial blood for an equal rise in oxygen uptake, particularly at the lower levels of exercise (Fig. 3 *B* and *C*). The patients with the greatest degree of limitation of cardiac output during exercise are those who show the greatest difference from the normal relationship.

Femoral venous blood saturation and lactic acid. The relationship found between the rise in the concentration of lactic acid in the arterial blood and the level of oxygen saturation in the femoral venous blood during the latter half of exercise is plotted in Fig. 4. In the subjects with normal cardiac outputs the concentration of lactic acid in the arterial blood increases almost

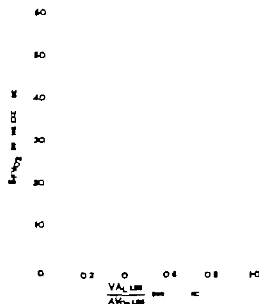


Fig. 5. The relationship of the mean femoral venous blood oxygen saturation to the ratio $VA_L/\Delta VO_2$ (milligrams of lactic acid produced per milliliter of oxygen used) in the legs between the fifth and tenth minutes of exercise. Symbols as in Fig. 3.

linearly as the femoral venous saturation falls below 40 per cent The values in the patients with heart disease again depart from the normal relationships to an extent which increases with increasing limitation of the cardiac output Thus the greater the disability the less is the rise in the concentration of lactic acid in the arterial blood at any given level of femoral venous blood saturation It is to be appreciated that in order to attain the lower levels of femoral venous saturation the subjects with normal or only moderately impaired cardiac-output responses have to carry out considerable exertion whereas the patients with severe heart disease attain these levels with relatively light exercise

Total oxygen uptake femoral venous blood saturation and lactic acid On the basis of the assumption that the arterial concentration of lactic acid is a fair measure of the production of lactic acid the data so far presented suggest not surprisingly that the production of lactic acid depends on the degree of exercise and increase in oxygen utilized and also on the degree of fall in oxygen tension in the exercising muscle In order to combine these two parameters in an attempt to measure the production of lactic acid it is necessary to know the influence of a fall in muscle oxygen tension on the production of lactic acid An estimate of the ratio of the production of lactic acid to the consumption of oxygen in the exercising limbs under varying conditions can be made as below

The two values in the latter ratio (1) are directly measured and the ratio expresses milligrams of lactic acid diffusing into the blood of the leg from the exercising muscle per milliliter of oxygen consumed by the leg The ratio is an over all value for all of the tissues of the limb and is not strictly confined to the metabolism of the muscles The muscles however certainly account for almost all of the metabolism under exercising conditions and furthermore even if there were a considerable increase in blood flow through relatively non metabolizing zones it would have little effect on the ratio Thus the ratio is analogous to the respiratory exchange ratio of expired air which is unaffected by the magnitude of dead space ventilation

The values of this ratio (femoral VA_L/femoral AV_{O_2}) during exercise are given in Table II The ratio during rest has not been calculated in view of the degree of error in the estimation of lactic acid in relation to the resting gradients The milligrams of lactic acid produced per milliliter of oxygen consumed in the leg during exercise are plotted against the femoral venous saturation in Fig 5 Once again the two variates are not entirely independent but their mathematical relationship would be such as to produce a positive correlation instead of the negative one observed A most interesting correlation is the considerable increase in the production of lactic acid (from < 0.1 mg to > 0.8 mg per milliliter of oxygen) as the femoral

$$\text{Leg blood flow } (\dot{Q}\text{ leg}) = \frac{\text{O}_2 \text{ consumption by legs } (\dot{V}_{O_2}\text{ leg})}{\text{AV oxygen difference in legs } (AV_{O_2}\text{ leg})}$$

Also

$$\dot{Q}\text{ leg} = \frac{\text{Rate of production of lactic acid in legs } (\dot{M}_L\text{ leg})}{\text{VA lactic acid difference in legs } (VA_L\text{ leg})}$$

Thus

$$\frac{\dot{V}_{O_2}\text{ leg}}{AV_{O_2}\text{ leg}} = \frac{\dot{M}_L\text{ leg}}{VA_L\text{ leg}}$$

And

$$\frac{\dot{M}_L\text{ leg}}{\dot{V}_{O_2}\text{ leg}} = \frac{VA_L\text{ leg}}{AV_{O_2}\text{ leg}}$$

venous saturation falls (from > 50 to < 10 per cent) It will be noted that even normal and mildly disabled patients with heart disease show this increase in the production of lactic acid per unit of oxygen consumed at higher levels of exercise and lower levels of femoral venous saturation It will also be noted that the greater is the impairment of the increase in cardiac output the lower are the levels of femoral venous blood saturation at which the production of lactic acid per unit of oxygen consumed increases It is tempting to suggest that this may be due to enzymatic adaptations However in previous studies of blood flow in the leg under these conditions evidence was given which suggests that the skin blood flow to the leg increases considerably during leg exercise in normal subjects and that it is only in the most disabled subjects that the skin blood flow to the leg remains at extremely low levels during leg exercise *Thus it is probable that saturation of the blood leaving the exercising muscle is of the order of the femoral venous saturation in only those patients with Grade III impairment of the cardiac output response to exercise* However this data can still be used to give an approximate estimate of the production of lactic acid at different levels of femoral venous saturation The regression equation for the prediction of lactic acid production as calculated from the data illustrated in Fig 4 is shown in Equation (2) below where S_{FV}^{ex} is the oxygen saturation of the femoral venous blood

If we wish to use this regression equation to calculate the amount of lactic acid produced in the exercising muscle during exercise then it would appear reasonable to employ the increase in the concentration of lactic acid in the arterial blood as a measure of the lactic acid produced by the exercising muscles and the increase in oxygen uptake as a measure of the oxygen consumed by the exercising muscles The equation then becomes that shown in Equation (3) below Thus we now have a relationship which makes allowances for both the increase in metabolism and the effect of the muscle oxygen tension on this metabolism It is unfortunate that neither femoral venous blood oxygen tension nor pH was measured but nevertheless in the range of blood oxygen saturation under consideration the relationship of saturation to oxygen tension is almost linear provided that changes in pH are not of a very sizable degree

When the increase in the concentration of lactic acid in arterial blood is plotted against the derivation of increase in total body oxygen uptake and femoral venous blood saturation described above a striking correlation is obtained (correlation coefficient r = +0.91) with all subjects and patients studied (Fig 6) There is no longer any important distinction between the normal subjects and the patients with varying degrees of cardiac disability Although more precise studies are needed there is at present no definite evidence that there is any fundamental difference

$$\frac{M_{L\,Leg}}{\dot V_{O_2\,Leg}} \text{ (mg lactic acid per ml } O_2 \text{ used)} = 0.69 - 0.011\, S_{FV}^{ex} \qquad (2)$$

$$\frac{\text{Increase of arterial lactic acid concentration during exercise}}{\text{Increase of } \dot V_{O_2}} = 0.69 - 0.011\, S_{FV}^{ex}$$

Bring S_{FV}^{ex} to unity/100 and rearrange

$$\text{Increase of arterial lactic acid concentration} = \text{Increase of } \dot V_{O_2} \left(\frac{63 - S_{FV}^{ex}}{100}\right) \qquad (3)$$

in the metabolism related to the production of lactic acid in exercising muscles in normal subjects and that in patients with heart disease

In Fig 6 it will be noted that 3 patients with Grade III impairment of the cardiac output response appear to have higher levels of arterial lactic acid than the general correlation would suggest It is of interest that these 3 subjects are the only ones in the whole series who had femoral venous blood saturations below 10 per cent during exercise It has been shown previously that the regional venous blood saturation of the whole arm[14] and of the splanchnic region may fall to levels well below 40 per cent (as low as 10 per cent) in such patients during exercise It is possible that under these conditions lactic acid may be produced in increased quantities in nonexercising muscles and even in other tissues

Concentration of lactic acid in arterial blood and production of lactic acid in exercising limbs It has been assumed by many workers that these values are reliably related The results of this study allow some further analysis of this assumption The amount of blood flowing through the exercising legs as estimated by the method of Donald and associates[8] is shown in Table V Because this estimate (admittedly approximate) is of considerable importance in this context it is worth briefly considering its validity It is calculated by the Fick principle as follows

Even quite considerable errors in the estimation of oxygen uptake in the resting leg which are unlikely will cause only small errors in the exercising blood flow values

During supine leg exercise on a bicycle ergometer the amount of work performed by muscles outside the leg is remarkably small and the assumption that almost all of the excess total body oxygen uptake (excess $\dot{V}_{O_2}$ exercise) is used in the legs is a reasonable one However the oxygen consumed by the iliopsoas and the respiratory muscles will cause a slight overestimate of the blood flow in the leg With regard to the exercising AV_{O_2} difference the assumption is made that the femoral AV_{O_2} difference is truly representative of all of the venous blood draining from the exercising leg

Multiplying the estimated blood flow in the leg ($\dot{Q}$ leg Table V) by the femoral lactic acid VA difference gives an approximate measure of the rate of diffusion of lactic acid into the blood flowing through the legs (M_L Table II) during exercise Again it is assumed that the femoral lactic acid VA difference is representative of that in all of the blood draining from the legs

It is now possible to relate this calculated rate of diffusion of lactic acid into the blood flowing through the legs to the rise in the concentration of lactic acid in arterial blood during exercise (see Fig 7) There is a direct relationship both in normal subjects and in all patients with

$$\dot{Q} \text{ exercising legs} = \frac{\dot{V}_{O_2} \text{ leg at rest} + \text{Excess total } \dot{V}_{O_2} \text{ exercise}}{AV_{O_2} \text{ exercising legs}}$$

The oxygen uptake of the legs in the resting state has been calculated by multiplying the estimated resting leg blood flow by the measured resting femoral AV_{O_2} difference The resting leg blood flow has been calculated from estimations of total leg blood flow at rest by plethysmography The values of resting leg blood flow in normal subjects and in cardiac patients with varying degrees of impairment of resting cardiac output used in these calculations have been gratifyingly close to recent unpublished measurements of leg blood flow by indicator dilution techn

varying grades of cardiac disability It should be noted that these two variates are again not entirely independent the concentration of lactic acid in arterial blood being employed in the determination of the femoral venous–arterial lactic acid concentration difference However their mathematical relationship would be such as to produce a negative correlation in contrast to the positive correlation observed It should be emphasized once more that even if the determination of the rate of ad of lactic acid to the blood flowing the exercising muscle were comp

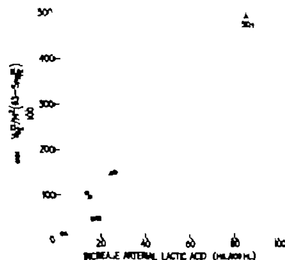


Fig 6 The relationship of the derived value (see text) of the increase in oxygen uptake and the femoral venous blood saturation to the increase in lactic acid concentration in arterial blood during leg exercise Symbols as in Fig 3

curate it does not necessarily measure the rate of production of lactic acid within the exercising muscles As already stated an abnormally low ratio of blood flow through liver (metabolism) kidney (excretion) and other tissues (diffusion and metabolism) to the blood flow through exercising muscle will prevent a normal degree of clearance of lactic acid from the blood and thus levels of arterial blood will be higher and the rate of diffusion of lactic acid from exercising muscle will be decreased If however a steady state could be demonstrated including a steady concentration of lactic acid in the exercising muscles then the true rate of production of lactic acid would be determinable

Concentration of lactic acid in arterial blood at rest The finding that the concentration of lactic acid in arterial blood during rest is normal in patients with severe heart disease even when they are in congestive failure is in agreement with that of Cotes Reports in the literature are at variance on this point and have been reviewed by Altschule[2] These resting observations are in accordance with the present findings during exercise which suggest that the production of lactic acid per unit of oxygen used is not increased until the venous saturation of the region is well below 40 per cent and the muscle venous blood is below 25 per cent In previous studies of regional venous blood saturations in patients with heart disease at rest saturations of this low order were not found even in the resting forearm muscle of patients with severe cardiac disability[7,1]

General considerations In the normal subjects there is only a slight rise in the concentration of lactic acid in arterial blood at the lower levels of exercise (see Fig 3) However as the degree of exercise increases (rise of oxygen uptake of over 300 ml/min/square meter) and the femoral venous saturation falls below 40 per cent (Fig 3) there is a considerable rise in the production of lactic acid per unit of oxygen used by the exercising muscle (Fig 4) Thus the production of lactic acid rises abruptly It was this abrupt rise in the production of lactic acid as exercise increases that led to the suggestion by Margaria Edwards and Dill[6] that there is an alactic phase at the lower levels of exercise in normal subjects In fact there is always an increase in the production of lactic acid at even the lowest levels of exercise

Finally it is of interest to consider further the ratio which describes the lactic acid produced per unit of oxygen used If one gram molecule of oxygen is considered to be equivalent to two grams molecule of lactic acid as suggested by Huckabee[6] then the ratio can be expressed as a pure fraction which if all muscle metabolism

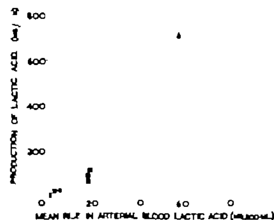


Fig 7 The relationship of the calculated rate of production of lactic acid in the exercising leg to the rise in the lactic acid concentration in arterial blood Symbols as in Fig 3

were that of carbohydrate would give some measure of the proportion of anaerobic to aerobic metabolism The fractions obtained in this way are remarkably small (see Table II) considering the undoubtedly low oxygen tension in the exercising muscles in a number of these investigations The highest figure obtained during exercise was 0 11 There is some difference of opinion concerning the oxygen equivalent of lactic acid under conditions of exercise but the reader can make the appropriate calculations from the data in Table II However it has now been shown that at rest at least the combustion of carbohydrate accounts for only a portion of the oxygen uptake of muscle It is unwise therefore to draw any definite conclusions from such calculations until all possible muscle metabolites are studied simultaneously

Summary

The concentrations of lactic acid in arterial and femoral venous blood have been measured in normal subjects and patients with heart disease during supine leg exercise on a bicycle ergometer Measurements of oxygen uptake and of arterial mixed venous and femoral venous blood oxygen saturation have been made at the same time

Patients with heart disease had a higher concentration of lactic acid in arterial blood than was found in normal subjects at similar levels of exercise and oxygen uptake This greater rise in the concentration of lactic acid in arterial blood is related to the degree of limitation of the cardiac output increase and to reduced blood flow in the leg and femoral venous saturation which occurred during exercise

It has been possible to calculate the production of lactic acid per milliliter of oxygen used by the exercising legs This value increases considerably as the femoral venous saturation (and presumably muscle oxygen tension) falls The regression equation derived from this correlation can be used to describe the relationship between the concentration of lactic acid in arterial blood the oxygen uptake and the femoral venous saturation This relationship holds good for both normal subjects and cardiac patients

An approximate estimate has been made of the blood flow in the leg during exercise and this has allowed the approximate order of lactic acid produced by the exercising muscles to be determined These calculated values correlate fairly well with the concentration of lactic acid in arterial blood

In a study of the concentration of lactic acid in the arterial blood of patients at rest in bed the concentration in severely disabled patients with heart disease was of the same order as that in patients without cardiorespiratory disease

Dr O L Wade (now Professor) gave valuable assistance during the early stages of this work

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The circulatory effects of hexadimethrine bromide (Polybrene) in dogs

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Hexadimethrine bromide (Polybrene) is a polymeric quaternary ammonium salt for which the empirical formula is $(C_{13}H_{30}Br_2N_2)_x$. It neutralizes the anticoagulant action of heparin both in vitro and in vivo and, according to Blumberg, Wintersched, Dillard, Vetto, and Merendino, it has the advantages over protamine sulfate of uniform potency, stability, less toxicity, less hypotensive effect, and a faster action. The presently agreed anticoagulant neutralizing dose of Polybrene is 1 to 2 mg. for each milligram of injected heparin.

No toxic effects were observed when Polybrene was injected intravenously in anesthetized nonheparinized dogs in a dose range of 1 to 5 mg. per kilogram of body weight (Kimura, Young, Stein, and Richards). However, these workers observed that larger doses of Polybrene were often associated with moderate reduction of the systemic arterial pressure and that very large doses of the drug, of the order of 30 mg. per kilogram of body weight, were uniformly fatal in these unheparinized animals; prior heparinization was found, however, to prevent these lethal effects until a much greater dose level was reached.

Lillehei, Sterns, Long, and Lepley[3] did not observe any toxic effects of the drug when it was injected rapidly in doses up to 12 mg. per kilogram of body weight intravenously in unanesthetized heparinized dogs, whereas Weiss, Gilman, Catenacci, and Osterberg[4] reported that Polybrene in a 1:1 neutralizing dose in heparinized dogs caused mild hyperpnea which increased with the rate of injection of the drug.

During clinical trials, Blumberg and associates found no hypotensive effect when the drug was slowly injected intravenously in human subjects. However, Weiss and co-workers[4] observed that the slow injection of diluted Polybrene in a heparin-neutralizing dose was associated with symptoms in 14 out of 30 heparinized patients. The symptoms appeared within a few minutes of the injection and included giddiness, wheezing, coughing, choking, tightness of the chest, burning sensation in the chest, facial flushings, lumbar backache, generalized sweating, weakness

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numbness of the arms and cramp of the legs. Blood pressure records taken at the time of the injection showed a fall in systemic arterial pressure of 10 to 50 mm. Hg in 7 of the patients. The blood pressure recovered rapidly in these subjects.

More recently, Rothnie and Kinmonth observed that the rapid injection of the drug in dogs was associated with an immediate reduction in the systemic arterial pressure. However, when slower injections of the drug were given to patients after cardiopulmonary bypass there was no change in the systemic blood pressure.

During experiments with the extracorporeal circulation in dogs we noticed that the rapid intravenous injection of undiluted Polybrene was immediately followed by an obvious dilatation of the right side of the heart associated with a marked fall in systemic arterial pressure. It seemed possible that these changes might be due to pulmonary hypertension induced by the drug, and the following report describes a series of experiments designed to study the effects of Polybrene on the systemic and pulmonary circulations of the anesthetized dog.

Material and methods

Laboratory techniques. Mongrel dogs of both sexes, of which the weights ranged from 7 to 37 kilograms, were anesthetized by intravenous sodium thiopentone (20 to 25 mg./Kg. of body weight) and maintained thereafter on a cyclopropane-oxygen mixture given through a closed circuit by endotracheal intubation and hand ventilation. The chest was opened by splitting the sternum, and a modified No. 9 double-lumen cardiac catheter was passed into the pulmonary artery via the right ventricle to allow pressure records and samples of blood to be taken simultaneously. Nylon catheters (2 mm. internal diameter) were passed directly into the left atrium, right atrium, and both femoral arteries, the latter to allow simultaneous arterial blood samples and pressure records. Pressures were recorded from each of these catheters by inductance manometers. The pulmonary arterial and left atrial pressures were arranged to allow direct differential records. Mean pressures were recorded by electrical integration. Zero reference point was the back of the dog in the supine position. Pressures were recorded by an ultraviolet recorder. Blood oxygen saturation was determined by a Brinkman hemoreflector, and blood oxygen capacity was measured by means of a Unicam densitometer calibrated against the method of Van Slyke. Arterial blood pH was determined according to the method of Wynn and Ludbrook.[6] Arterial pCO_2 was derived from the Singer and Hastings[7] nomogram, using the foregoing pH measurement, and the CO_2 content was measured according to the method of Van Slyke and Neill.[8] Blood transfusion was given at the time of sampling to replace the measured loss of blood.

Plan of investigation. The experiment was designed to demonstrate the circulatory effects of both the rapid and slow intravenous injections of undiluted Polybrene. All of the dogs in the three groups were heparinized by a dose of 3 mg. per kilogram of body weight.

Group I (6 dogs). After the initial procedures of anesthetization, operation, heparinization, and positioning of the various catheters, phasic and mean pressures were recorded from the various sites during a 2 minute control period. Arteriovenous blood oxygen content difference (A-V diff.) was measured at the beginning and end of this period, and at the same time arterial pH and pCO_2 were determined. Blood oxygen capacity was measured 1 minute after the start of the control period and this value was used for the calculation of the A-V diff. during that period and also for the A-V diff. at 1 minute after the injection of Polybrene. Fifty milligrams (5 ml.) of undiluted Polybrene was then injected into a peripheral vein within 4 to 10 seconds. Pressure records were made throughout the period of injection and continued for 5 minutes thereafter. Samples of blood were taken for measurements of A-V difference at 1 minute after the injection and again during the recovery period at 5 minutes, at which latter time the pH and pCO_2 were also determined. Blood oxygen capacity was measured during the recovery period, and the value was used for calculating the A-V diff. at that time. Two further experiments were then carried out in an identical manner with injections of 50 mg. of Polybrene on each

occasion The control period in these two subsequent experiments was the recovery period of the preceding experiment

Group II (4 dogs) Curarization with 5 to 10 mg of d tubocurarine intravenously was performed at the time of the anesthetization otherwise the initial procedures were carried out as in the previous experiment including the measurements and determinations during the control period up to the point of injection of Polybrene The undiluted drug was then infused into a peripheral vein in a dose of 50 mg per minute for 3 minutes Pressures were recorded during the injection of Polybrene throughout the postinjection period for 5 minutes and then during a 3 minute recovery period A V differences were determined at minute intervals during the 3 minutes of the injection and again during the recovery period Blood oxygen capacity was measured during the second minute after the start of the injection of Polybrene and this value was used for the calculation of the A V differences during the infusion The blood oxygen capacity was again determined during the 3 minute recovery period Also measured were pH and pCO_2 at 1 minute after the start of the infusion and again during the recovery period

Group III (7 dogs) This group of animals was used as a control experiment to demonstrate the acute effects of injections of the same volume of normal saline as in the dogs of Group I The experimental protocol was identical to that described for the dogs of Group I except that saline was substituted for the first and third injections of the drug and the second injection was of 50 mg of Polybrene

Results

Group I A representative record of the vascular pressures of a heparinized dog after the rapid intravenous injection of 50 mg of undiluted Polybrene into a peripheral vein is shown in Fig 1

The average mean pulmonary arterial pressure during the control period was 11 mm Hg In all of the experiments the pulmonary arterial pressure started to increase between 4 and 10 seconds after the start of the injection of Polybrene and an average maximal increase of 14 mm Hg was reached after 8 to 32 seconds The individual maximal increases in the mean pulmonary arterial pressure in all experiments are shown in Fig 2

The average mean femoral arterial pressure during the control period was 82 mm Hg In all instances the femoral arterial pressure started to fall between 6 and 14 seconds after the start of the injection and reached an average maximal reduction of 40 mm Hg after 13 to 44 seconds Individual maximal changes in the mean femoral arterial pressure are shown in Fig 2 The average of the maximal changes in mean vascular pressures after the first second and third injections of Polybrene are presented in Table I The average of the changes in the mean femoral and pulmonary arterial pressures after Polybrene in the first and second injections and the time relationships are shown in Fig 3 The average percentage change in these pressures in all 18 experiments and the time relationships are presented in Table II

The increase in pulmonary arterial pressure always preceded the fall in systemic arterial pressure by 2 to 4 seconds The average mean left atrial pressure during

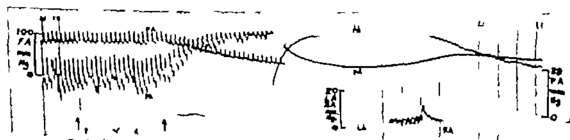


Fig 1 A representative record of the vascular pressures of heparinized dog after the rapid intravenous injection of 50 mg of undiluted Polybrene

Table I The circulatory effects of rapid intravenous administration of Polybrene The average (range in parentheses) of the maximal changes in mean vascular pressures after the first second and third injections of Polybrene in 6 dogs

	Control pressures (mm Hg)				Changes in pressure after Polybrene (mm Hg)			
	RA	PA	LA	FA	RA	PA	LA	FA
First injection of Polybrene	4 (1 7)	12 (10 17)	7 (5 11)	96 (65 143)	+1 (−1 to +9)	+11 (+6 to +17)	−2 (0 to −6)	−36 (−17 to −50)
Second injection of Polybrene	3 (0 6)	10 (9 12)	6 (5 8)	82 (72 98)	+2 (0 to +6)	+14 (+10 to +19)	−3 (−1 to −5)	−48 (−21 to −72)
Third injection of Polybrene	5 (2 10)	10 (7 13)	6 (4 8)	69 (38 100)	+3 (+1 to +7)	+15 (+10 to +23)	−3 (−1 to −5)	−36 (−10 to −55)

Table II The average percentage changes in PA and FA pressures after rapid intravenous administration of Polybrene and their time relationships

	Average percentage rise in mean pressure	Average time to start of rise (sec)	Average time to peak (sec)	Average time to reestablishment (sec)
Pulmonary artery	135% (50–220%)	7 6 (4 10)	19 7 (8 32)	74 4 (42 148)

	Average percentage fall in mean pressure	Average time to start of fall (sec)	Average time to peak fall (sec)	Average time to reestablishment (sec)
Femoral artery	34% (20–82%)	9 8 (6–14)	26 4 (13–44)	81 (31 220)

O[illegible] occa[illegible] the pulmonary arterial pressure did not return to pre-injection [illegible] after [illegible] The [illegible] results [illegible] these percentages [illegible]
The range of results is given in parentheses

the control period was 7 mm Hg After Polybrene the mean left atrial pressure was reduced in all experiments except one in which it did not change The average mean left atrial pressure recorded at the peak of the rise in the pulmonary arterial pressure was 4 mm Hg an over all reduction of 3 mm Hg

The average pulmonary arterial–left atrial pressure gradient before Polybrene was 4 mm Hg After the rapid intravenous injection of the drug this pressure gradient increased in all experiments The average maximal increase was 16 mm Hg These results are illustrated graphically in Fig 2 The average mean right atrial pressure during the control period was 4 mm Hg After injection of Polybrene at the time of the maximum increase in pulmonary arterial pressure the mean right atrial pressure was increased in 11 of the 18 experiments The mean right atrial pressure was unchanged in 6 instances and in one experiment it was reduced by 1 mm Hg The average mean right atrial pressure in the 11 experiments in which it increased

recorded at the time of the maximum rise in the pulmonary arterial pressure was 7 mm Hg an average increase of 4 mm Hg

The mean arterial oxygen saturation during the control period was 98 per cent One minute after the injection of Polybrene at a time when pulmonary arterial pressure was considerably elevated mean arterial oxygen saturation was 97 per cent

In 2 animals the injection of Polybrene was associated with an increasing degree of arterial oxygen unsaturation with successive injections

The blood oxygen capacity during recovery after injection of Polybrene showed a mean increase of 0 44 volumes per cent as compared with the values in the control period

The mean A V diff during the control period was 7 23 volumes per cent One minute after injection of Polybrene the changes in A V diff were variable In 4 of the 6 dogs the mean increase in A V diff was 0 25 volumes per cent In 2 dogs there was a much greater change in A V diff particularly with successive injections of Polybrene These large changes in A V diff were associated in these 2 animals with considerable arterial oxygen unsaturation

In 4 of the 6 dogs the systemic arterial pH and pCO_2 were not significantly changed throughout the duration of the experiment which included three successive injections of Polybrene However in one dog the arterial pH fell and the pCO_2 progressively increased with successive injections of Polybrene These changes in this dog were associated with progressive oxygen unsaturation In one other dog the arterial pH fell and the pCO increased after the first injection but thereafter remained unchanged

The heart was observed closely during the period of each injection of Polybrene Shortly after the completion of the injection considerable dilatation of the right heart was observed on every occasion this dilatation coincided with the rise in pulmonary arterial pressure Successive injections of Polybrene were associated with progressive increases in the size of the right heart It was observed that the dilatation of the right heart was much slower to remit than was the elevation in the pulmonary arterial pressure

Group II During the control period the average mean pulmonary arterial pressure was 18 mm Hg *During the infusion of* Polybrene (50 mg per minute for 3 min

Table III The circulatory effects of slow infusion of Polybrene (50 mg per minute for 3 minutes)

Dog No.	Dog Weight (kg)	State and duration of injection	Pressures (mm Hg) R.A	P.A	L.A	F (	Blood oxygen capacity (Vol %)	Oxygen saturation (per cent) Art	M.V.B	A V diff (vol %)	pH	pCO_2 (mm Hg)
1	21 75	Control	—	21	12	82	18 94	96	60	6 82	5 7	22
		Polybrene	—	27	12	54	17 14	97	54	7 37	7 616	18
2	23 15	Control	9	20	13	100	17 47	93	50	7 51	7 4 0	6
		Polybrene	9	27	11	47	16 63	93	37	9 37	7 480	25
		Recovery	10	23	12	8	17 16	89	34	9 44	7 450	26
3	17 35	Control	2	16	9	119	20 24	98	63	7 12	7 486	24
		Polybrene	4	19	10	100	19 05	97	57	7 6	7 480	24
		Recovery	3	16	8	78	20 52	98	58	8 70	7 476	24
4	19 2	Control	2	16	9	77	17 46	98	72	4 51	7 370	23
		Polybrene	3	16	5	55	16 88	98	71	4 56	7 387	22
		Recovery	1	12	4	69	16 72	97	6	5 83	7 406	21

[illegible] Dog 1 [illegible]

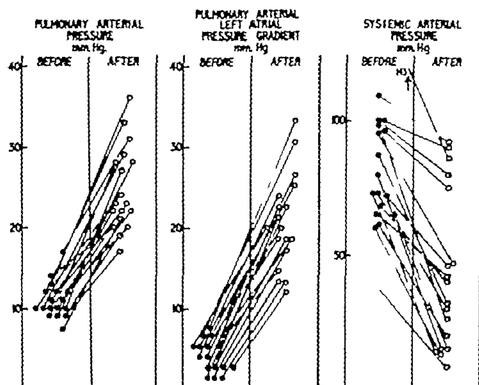


Fig. 2. Mean vascular pressures before and after the rapid intravenous injection of Polybrene.

utes) 3 of the 4 dogs showed a small increase in pulmonary arterial pressure. The increase in the mean pulmonary arterial pressure in these 3 dogs was 6, 7, and 3 mm. Hg. In the other animal (No. 4) no change was observed.

During the control period the average mean femoral arterial pressure was 95 mm. Hg. During the infusion of Polybrene the femoral arterial pressure was reduced in all 4 dogs; the mean average maximum reduction was 31 mm. Hg.

Neither right nor left atrial pressure showed any consistent trend during infusion of Polybrene as compared to the control period, and the maximum change observed was 4 mm. Hg (see Table III).

The mean arterial oxygen saturation during the control period was 96 per cent and remained unchanged during the infusion of Polybrene.

The mean blood oxygen capacity during the control period was 18.50 volumes per cent. The blood oxygen capacity determined 2 minutes after the start of the infusion of Polybrene showed a mean decrease of 1.05 volumes per cent as compared with the values of the control period.

The mean A-V diff. during the control period was 6.49 volumes per cent. During the 3 minute period of infusion of Polybrene the A-V diff. increased in all dogs; the mean increase was 0.74 volumes per cent. In all of the dogs the systemic arterial pH and pCO_2 remained relatively unchanged throughout the experiment (see Table III).

The heart was observed closely throughout the period of infusion of Polybrene. Within 1 or 2 minutes of the commencement of infusion the right heart was noticed to be increasing in size, and as the infusion continued this dilatation became progressively more conspicuous until both the right ventricle and right atrium appeared to be grossly overdistended. This occurred in all 4 dogs although the changes in the pulmonary arterial and right atrial pressures were small.

Group III. Rapid injections of 5 ml. of normal saline in 7 dogs failed to show any measurable effects on the pulmonary arterial, left and right atrial, and systemic arterial pressures. A subsequent injection of 5 ml. of undiluted Polybrene given under the same experimental conditions a in

the dogs of Group I consistently caused a similar rapid but transient elevation of the pulmonary arterial pressure without change in the left atrial pressure. An additional injection of 5 ml of normal saline after the dogs had recovered from this injection of Polybrene again failed to show any change in the right or left heart pressures. This demonstrates the absence of measurable effects due to the rapid intravenous injections of 5 ml of normal saline although 5 ml of Polybrene injected under identical conditions produced marked circulatory changes.

Discussion

These experiments have shown that the rapid intravenous injection of undiluted Polybrene in doses commonly used therapeutically consistently produced a considerable increase in the pulmonary arterial pressure in heparinized anesthetized open chest dogs. This rapid but transient elevation of the pulmonary arterial pressure was reproducible in the same animal with successive injections. The pulmonary arterial left atrial pressure gradient was considerably increased in all experiments; the left atrial pressure usually was reduced. This increase in pressure gradient could have been caused by an increase in the vascular resistance or by a very considerable increase in the right ventricular output. Since oxygen uptake was not determined, measurements of blood flow are not available. However, the following considerations suggest that the increase in pulmonary arterial pressure was due to increased resistance rather than flow. First, a considerable increase in pressure gradient across the lungs was consistently produced after Polybrene despite variable changes in the arteriovenous oxygen content difference. Secondly, the right heart showed a marked dilatation during this acute phase concomitant with the abrupt increase in the pulmonary arterial pressure, and this dilatation was often associated with a small increase in the right atrial pressure. The occurrence of a marked fall in systemic arterial pressure a few *seconds* after the increase in pulmonary arterial pressure again suggests a failure of flow due initially to acute right heart embarrassment.

The control studies in which the rapid intravenous administration of the same volume of normal saline was used instead of Polybrene show that the volume effect of the injection was negligible.

The effect of continuous but much slower infusion of the drug on the pulmonary arterial pressure was much less marked and the main effect observed was acute right heart dilatation accompanied by a profound systemic arterial hypotension. This observation in the light of the previous experiments with acute injections of the drug suggests a mechanism of action that is not confined to its pulmonary vascular effects. The acute right heart dilatation accompanied by a marked fall in the *systemic arterial pressure with only* a small increase in the pulmonary arterial pressure suggests that myocardial performance was being influenced by either a direct toxic effect or an indirect neurohumoral mechanism. Although these effects of the drug on the pulmonary circulation have not been recorded previously, the observed reduction of the systemic arterial

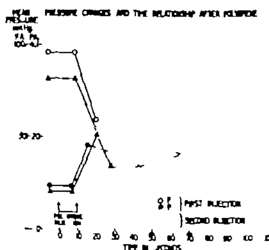


Fig. 3. The average of the changes in mean maximal systemic and pulmonary arterial pressures after the first and second rapid intravenous injections of Polybrene are plotted against time. The changes in pressure and the time relationships after the third injection are not plotted but are not substantially different from those after the second injection. After the first injection of Polybrene in one dog the pulmonary arterial pressure did not return to normal until after 9 minutes. This exceptionally long time was omitted when calculation made of the percentage time of reestablishment after the first injection.

pressure confirms the similar observation recently reported by Rothnie and Kinmonth.[5] The only other work which has any relevance to the present experiments is that of Weiss and co-workers who observed that the intravenous infusion of diluted Polybrene in human subjects was often accompanied by systemic arterial hypotension dyspnea and sensations of distress which could possibly be explained on the basis of these findings

Although these experiments have been carried out in the anesthetized open-chest dog the consistency of the findings and the fact that the doses of drug were within the range of those normally used therapeutically compel the authors to advise caution in the use of this drug particularly if it is given rapidly by the intravenous route

Summary

1 The effects of both rapid and slow intravenous injections of undiluted Polybrene on the pulmonary and systemic circulations of anesthetized heparinized open-chest dogs have been studied

2 The rapid injection of 50 mg of Polybrene was followed by an abrupt increase in the pulmonary arterial pressure associated with a fall in the left atrial pressure an increase in the right atrial pressure and a reduction of the systemic arterial pressure in all of the animals studied Successive injections of the same amount of the drug produced an identical pattern of response

3 With slower injections the effects on the pulmonary arterial pressure were not so marked but acute right heart dilatation was still observed

4 The evidence from these experiments suggests that the effects of the drug are probably twofold in that it increases the pulmonary vascular resistance at a site which at present is undetermined and in addition appears to cause acute right heart dilatation which may be due in part to a depressant action on the myocardium

We are grateful to Professor Donald and the staff of the Department of Medicine and also to the staff of the Department of Anaesthetics Royal Infirmary Edinburgh for their invaluable assistance in these studies We are particularly grateful to Dr S H Taylor of the Department of Medicine for his helpful advice and criticism in the preparation of this paper Mr J Walker and Mr W Jamieson of the Cardiopulmonary Bypass Unit and Mr J Ramsay and Miss Helen MacGregor of the Department of Medicine gave invaluable technical assistance

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Pulmonary and renal circulatory adjustments to the upright posture in patients with mitral valvular disease

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Orthopnea, i.e., breathing associated with effort in the recumbent position, is a common symptom in left heart disease as a consequence of disordered pulmonary circulatory hemodynamics. Even if respiratory and cerebral factors have been implicated as the origin of orthopnea, much interest has been directed to define the pulmonary hemodynamic derangement. Thus it still remains disputed whether orthopnea is caused by an increase in the pulmonary blood volume or by an increase in the pulmonary blood pressures leading to extravasation of fluid as the cranial part of the body is lowered. Also a possible change in renal hemodynamics and the renal handling of water and electrolytes leading to retention of fluid must be considered. In the present report the orthostatic circulatory changes are described in patients with mitral valvular disease. The cardiac output, the cardiopulmonary blood volume, and pressures in the pulmonary and systemic circuits were determined in patients in the recumbent posture (180 degrees) and when tilted to 45 or 60 degrees from the horizontal. In addition, the glomerular filtration rate, the renal blood flow, and the urinary excretion of sodium were measured simultaneously. The patients were selected to represent varying degrees of heart involvement, ranging from those who were virtually free of symptoms to those with chronic congestive failure.

Material

Ten patients with mitral valvular disease were selected for study, 8 women and 2 men. Aortic valvular disease was present in Patient No. 473. Six had sinus rhythm and 4 had atrial fibrillation. The heart size ranged between 400 and 1,060 ml. per square meter of body surface area. When grouped according to the New York Heart Association, 2 of the patients were in Group II, 7 in Group III, and 1 in Group IV. The clinical data are listed in Table I.

Methods

All patients were studied in the morning, recumbent and in the postabsorptive state. Sodium Amytal 0.1 Gm. was administered 2 hours before the start of the study. The pulmonary artery was catheterized according to Cournand, and an indwelling needle was placed in the brachial artery.

[illegible]
[illegible]
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Table I. Clinical data in 10 patients with rheumatic heart disease

Case number	Sex	Age (yr.)	Group (N.Y. Heart Assn.)	Rhythm	Heart size (ml./M.² BSA)	Right heart failure	Digitalis	Diagnosis	Orthopnea
567	F	32	III	SR	500	–	+	MS	+
597	F	49	III	AF	630	–	+	MS MI	+
632	F	36	II	SR	500	–	+	MS op	–
349	F	50	III	AF	730	–	+	MS MI	+
408	F	40	III	SR	400	–	+	MS	–
473	M	21	III	SR	750	–	–	AI MI	–
475	F	51	III	AF	800	–	+	MI	+
387	M	31	IV	AF	1,060	+	+	MS MI	+
801	F	28	III	SR	580	+	+	MI	+
93	F	28	II	SR	400	–	–	MS	–

*Tilted head down 30 degrees.
SR, Sinus rhythm; AF, Atrial fibrillation; MS, Mitral stenosis; MI, Mitral insufficiency; AI, Aortic insufficiency; MS op, Mitral stenosis operated by mitral commissurotomy.

The pressures in the pulmonary circuit were measured, including the pulmonary arterial wedged pressure (PCV).[4] Then the patient was allowed to rest for 30 minutes. Thereafter, the cardiac output was determined using the direct Fick principle with simultaneous sampling of blood from the pulmonary and brachial arteries and collection of expired air in a Tissot spirometer for 2 minutes. Pressures were then recorded again and the catheter was advanced to the wedged position. During continuous registration of pressures the patient was tilted to a position of 45 or 60 degrees from the horizontal (head up) and left there for about 30 minutes.[6] After the patient had been in the tilted position for 10 minutes, the catheter was withdrawn to the pulmonary artery, as judged from the pulse contour. The cardiac output was determined again, the catheter withdrawn to the right atrium, and, under pressure recording, the patient tilted back to the horizontal position. In some studies measurements were repeated after the patient had been in the horizontal position for 30 minutes.

One patient (No. 793) was tilted 30 degrees head down. No symptoms appeared in this position. The same measurements as in the other studies were made.

In 7 patients the cardiac output was also determined by the Stewart-Hamilton technique, and the total and the cardiopulmonary blood volumes[7] in the recumbent and in the upright postures were calculated.

In all patients the procedure was combined with the determination of renal clearances for para-aminohippurate and inulin, and the excretion of sodium was also determined. The clearance periods were generally between 15 and 30 minutes. The details of these techniques have been described before.

The blood gases were analyzed according to Van Slyke[8] and the expired air according to Haldane.[9] Blood pressures were

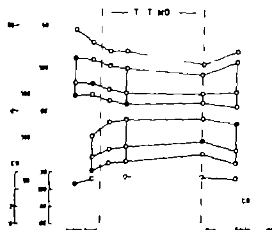


Fig. 1. This graph shows the effect of tilting (head up 60 degrees) in a patient with mitral valvular disease and right heart failure (Case 387). RA = right atrial; PA = pulmonary arterial; BA = brachial arterial pressures in mm. Hg; CO = cardiac output in liters per minute; HR = heart rate.

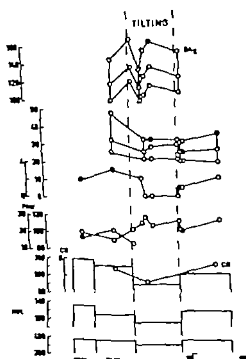


Fig 2 This graph shows the effect of tilting (head up 60 degrees) in patient with mitral valvular disease without evidence of right heart failure (Case 475) *BA* = brachial arterial *PA* = pulmonary arterial *RA* = right atrial and *PW* = pulmonary arterial wedged pressure in mm Hg *HR* = heart rate *CO* = cardiac output, in liters per minute *N* = urinary excretion of sodium *Inul* clearance and the renal clearance of *PAH* (para amino-hippurate)

registered with electromanometers either the Hansen and Warburg capacitance manometer[11] or an Elema strain gauge and inscribed on an Elema electrocardiograph Mean pressures were calculated from electrically integrated curves

As reference point for the pressures the horizontal level 5 cm below the angle of Louis was used in the recumbent position and the horizontal level about 3 cm above the apex beat was used in the tilted position The manometers were adjusted to correspond to both of these points when the pressures were continuously recorded during the change in the position of the patients

Results

The values for blood pressures and blood flow obtained when the patients were in the recumbent and upright positions are given in Table II The patients are divided into three groups according to the derangement of the circulation and the severity of the heart disease The first group contains 3 patients with moderately elevated pulmonary pressures (Nos 567 597 and 632) and almost normal cardiac outputs (arteriovenous oxygen difference below 50 ml L of blood) The second group contains 4 patients with elevated pulmonary pressures (pulmonary wedged pressure above 20 mm Hg) low cardiac outputs (Nos 349 408 473 and 475) (arteriovenous oxygen difference above 50 ml/L of blood) and no signs of right heart failure as judged either clinically or from the level of the right atrial pressure Finally the third group consists of 2 patients with clinical signs of right heart failure Both had very high pulmonary pressures but the blood flow was normal in one and low in the other The patient who was tilted head down (No 793) is presented last

On the whole the right atrial and pulmonary arterial wedged pressures decreased This was most marked in the third and second groups and less in the first wherein some patients even had virtually unchanged filling pressures The pulmonary arterial pressure decreased slightly in some of the patients in the second and third groups but was otherwise unchanged and

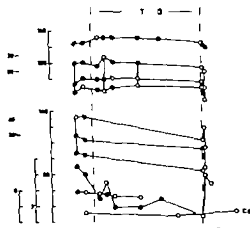


Fig 3 This graph shows the effect of tilting (head up 60 degrees) in patient with mitral valvular disease with marked pulmonary hypertension (Case 408) *BA* = brachial arterial *PA* = pulmonary arterial *RA* = right atrial and *PAW* = pulmonary ... pressure in mm Hg *HR* = heart ... output in liters per minute

Table II *Blood flow and blood pressures in 10 patients with mitral valvular disease*

Case number	Heart rate		A V O difference (ml /L)		Cardiac output (L /min)		Stroke volume (ml /beat)		Right atrium u	
	R	T	R	T	R	T	R	T	R	T
567	71	82	36	48	6 5	4 9	91	60	0	1
597	85	118	54	85	4 3	2 7	1	23	1	—
632	102	130	35	42	7 0	6 4	79	66	1	1
349	72	65	62	83	2 6	2 1	36	32	4	—
408	121	130	56	67	3 2	3 0	26	23	1	−3
473	108	107	56	61	5 5	4 9	51	46	3	−2
475	91	112	54	75	4 8	3 4	53	30	3	0
387	112	114	112	110	2 2	2 4	20	21	16	11
801	90	90	49	49	6 0	6 0	67	67	5	5
793	70	86	34	37	5 5	5 7	79	66	2	0

*Tilted head down 30 degrees R = recumbent and T = tilted (head up 60 degrees) position S = systolic D = diastolic and

the brachial arterial pressure usually increased The pulse pressure both in the pulmonary and systemic circulations usually decreased The systemic arterial pressure usually increased

In all patients except the 2 who were in right heart failure the cardiac output decreased when the upright position was taken This was reflected by an increase in arteriovenous oxygen difference The heart rate likewise increased and the stroke output decreased markedly In contrast in the 2 patients in right heart failure the cardiac output the arteriovenous oxygen difference the heart rate and the stroke volume did not change

Table III contains the data obtained by the dye method The total blood volume was definitely increased in 1 case (No 387) a patient who was in right heart failure The cardiopulmonary blood volume decreased in 3 cases (Nos 349 473 and 387) being essentially unaltered in the other 4 cases The fall in cardiopulmonary blood volume was observed in 3 out of 4 instances where this volume constituted more than 20 per cent of the total blood volume

Table IV contains the values for renal plasma flow glomerular filtration rate and excretion of sodium In the patients who were tilted head up the renal plasma flow glomerular filtration rate and excretion of sodium decreased whereas in the patient tilted head down they tended to increase The differences in the various circulatory parameters are shown in Table V

Fig 1 shows the course of events in one patient (No 387) with right heart failure Fig 2 in one patient (No 475) without heart failure and Fig 3 in one patient (No 408) with marked pulmonary hypertension

Discussion

The change from the horizontal to the upright position leads to a redistribution of blood volume and blood flow in the circulatory system for maintaining homeostasis The decrease in venous return is reflected by a fall in the cardiac output and a rise in the heart rate [2,3] At this stage compensatory mechanisms enter the circulatory system to maintain an adequate cerebral blood flow [14] Blood flow through other regions of the body is reduced part of the blood volume is redistributed to the central venous channels as arterial and venous constriction ensues Such homeostatic mechanisms are reinforced in the passive standing posture and when inadequate the subject may faint especially if the total blood volume is lowered for some reason Indeed physically trained individuals with a blood volume of good size generally show fewer reactions to orthostasis than do those not physically fit

It has been demonstrated that veno

Pulmonary wedge M		Pulmonary artery				Brachial artery			
		R		T		R		T	
R	T	S/D	M	S/D	M	S/D	M	S/D	M
19	15	47/18	27	37/2?	28	95/56	73	106/78	89
17	17	39/21	27	36/23	28	165/106	127	167/128	145
14	15	36/17	26	44/19	31	134/61	83	141/72	95
23	17	54/17	26	29/13	19	140/95	112	137/100	121
38	32	133/85	104	105/66	94	111 80	91	105/80	87
28	17	47/22	34	26/10	21	140/7	100	153/73	103
21	13	47/25	32	32/21	28	144/98	117	159/110	131
—	—	110/6)	82	93/60	71	101/61	77	12 /81	96
36	24	75/33	50	74/33	50	132/83	101	124/80	97
—	—	18/	11	16/	10	105/62	78	100/55	0

Blood pressures (mm Hg)

M = mean pressure

Table III Cardiac output total blood volume mean cardiopulmonary circulation time cardio pulmonary blood volume and hematocrit in 8 patients with mitral valvular disease

Case number	BSA	Hct ( )		TBV/1 73 M		CO		Mct		CPV/1 73 M		CPV/TBV (%)	
		R	T	R	T	R	T	R	T	R	T	R	T
567	1 59	36	36	5 10	4 86	5 17	4 04	6 7	11 5	0 6	0 84	12 2	17 2
597								18	19 9				
632	1 49	38	37	4 85	4 66	5 49	4 34	7 5	8 7	0 80	0 73	16 5	15 7
349	1 39	44	44	6 94	6 13	3 80	3 30	24 0	21 4	1 87	1 46	27 0	23 9
408	1 43	42	40	4 92	4 51	3 36	2 97	13 1	15 0	0 88	0 88	17 9	19 6
473	1 81	36	36	6 57	6 81	4 78	3 98	22 8	22 0	1 74	1 40	26 5	20 6
475	1 77	40	40	5 34	5 98	4 39	3 70	21 3	28 2	1 53	1 47	28 6	21 6
387	1 64	46	46	7 58	7 4	2 38	2 12	17 9	37 4	1 58	1 20	20 8	15 5

R = recumbent and T = tilted position (head up) CO Cardiac output (liters/minute) TBV Total blood volume (liters) M Mean cardiopulmonary circulation time (seconds) CPV Cardiopulmonary blood volume (liters) by the dye method H Hematocrit BSA Body surface area (square meters)

Table IV The renal clearance of PAH (para aminohippurate) and inulin (in ml per minute) and the urinary excretion of sodium (in mEq per liter) in 8 patients with mitral valvular disease

Case number	PAH			Inulin			Na excretion		
	R	T	Rec	R	T	Re	R	T	Rec
597	246	188	258	73	51	85	37	13	26
632	357	259	408	113	89	104	268	161	225
408	212	197	20	79	75	71	16	18	26
473	330	291	335	103	93	100	157	133	164
47	358	293	353	121	92	118	130	81	104
387	94	84	78	69	59	53	—	—	—
801	243	267	389	44	47	56	85	53	92
93	453	474	578	97	100	129	285	372	502

R Recumbent T Tilted (head up) Rec Recumbent after tilt

Table II Blood flow and blood pres ure in 10 patient with mitral val ular disea

Ca m ber	H r ate		A V O d ff n (ml L)		Cardiac output (l /min)		Strok v l m (ml /beat)		R ght atrium M	
	P	T	P	T	I	T	P	T	I	T
47	71	82	3f	4	6 5	4 9	93	60	0	1
5f	85	118	54	85	4 3	2 7	51	23	1	—
32	10?	139	35	42	7 0	4	9	6f	1	1
34	2	f	62	83	2 6	2 1	3f	32	4	—
408	121	139	5f	67	3 2	3 0	2f	23	1	−3
3	10	107	5f	3	5	4	51	4f	3	−2
47	91	112	54	7	4 8	3 4	53	30	3	0
3	112	114	112	110	2 2	2 4	20	21	1f	11
401	90	80		4	6 0	6 0	7	7	5	5
3	0		34	37	5	7		6f	2	0

*Tilted head down 10 degrees P = recumbent and T = tilted head up 60 degrees position — ry D — d 9r ad

the brachial arteri l pre sure usually in creased Th pulse pressure both in the pulmonary and sy temic circul tions u u ally decreased The systemic rterial pressure u ually increased

In all patients except the 2 who were in right heart failure th cardiac output decreased when the upri ht position w s taken Thi w s reflected by an increase in arteriovenous oxygen difference The heart rate likewi e increa ed and the stroke output decreased markedly In contrast in th 2 patients in right heart failure the cardia output th arteriovenous oxy en differe ce the heart rate and the stroke olum did not change

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Table IV cont ins th valu s for ren l plasma flow glomerul r filtration rate and excretion of sodium In the patients who were tilted head up the renal pl ma fl w glomerular filtration rate and excretion of sodium decreased whereas in the patient tilted head down they tended to increase The differences in the various circulatory p r meters are shown in Tabl V

Fi 1 shows the course of events in one pati nt (No 387) with right heart failure Fig 2 in one patient (No 473) without he rt failure and Fig 3 in one patient (No 408) with m rk d pulmonary hyper tension

Discussion

The change from the horizont l to the upright po iti n l ads to a redistribution of blood v lume and bl od flow in the circul tory system for m int ining homeo stasis The decre se in venous return is reflected by a f ll in the cardiac output and a rise in the he rt r te [11,12,13] At this stage compen atory mechanisms enter the cir culatory s stem to m int in n dequ te cerebr l blood flow [14] Bl od flow throu h other regions of the body is reduced part f the blood v lume is redi tributed to th central venous ch nnels rterial and venous constriction ensues Such homeo st tic me hanisms are reinforced in th pr ssive standin posture and when in adequ te the subject m y f int e pecially if the tot l blood volume is lowered for some reason Indeed phy ic lly tr in d individu ls with a l rge blood v lume of g od size generally sh w fewer re ctions to orthost t s th n do those not phy ic lly fit

It h s been demonstr ted th t ven

Blood pressures (mm Hg)

P lmonary edge M R	*P lmonary edge* M T	*Pulmonary artery* R S/D	*Pulmonary artery* R M	*Pulmonary artery* T S/D	*Pulmonary artery* T M	*Brachial artery* R S/D	*Brachial artery* R M	*Brachial artery* T S/D	*Brachial artery* T M
19	15	42/18	27	37/22	28	95/56	73	106/78	89
17	17	39/21	27	36/23	28	165/106	127	167/128	145
14	15	36/17	26	44/19	31	134/61	83	141/72	95
23	17	54/17	26	29/13	19	140/95	112	137/100	121
38	32	133/85	104	105/66	94	111/90	91	105/80	87
28	17	47/22	34	26/10	21	140/75	100	155/73	103
21	13	47/25	32	32/21	28	144/98	117	159/110	131
—	—	110/69	82	93/60	71	101/61	7	122/81	96
36	24	75/33	50	74/33	50	132/83	101	124/80	97
—	—	18/5	11	16/5	10	103/62	8	100/55	70

M = mea p es re

Table III Cardiac output total blood volume mean cardiopulmonary circulation time cardio pulmonary blood volume and hematocrit in 8 patients with mitral val ular disease

Case number	BSA	Hct ( ) R	Hct ( ) T	TBV/1 73 M R	TBV/1 73 M T	CO R	CO T	Mct R	Mct T	CPV/1 73 M R	CPV/1 73 M T	CPV/TBV (%) R	CPV/TBV (%) T
567	1 59	36	36	5 10	4 80	5 17	4 04	6 7	11 5	0 6	0 84	12 2	17 2
597								18 2	19 9				
632	1 49	38	37	4 85	4 66	5 49	4 34	7 5	8 7	0 80	0 73	16 5	15 7
349	1 39	44	44	6 94	6 13	3 80	3 30	24 0	21 4	1 87	1 46	7 0	23 9
408	1 43	42	40	4 92	4 51	3 36	2 92	13 1	1 0	0 88	0 88	17 9	19 6
473	1 81	36	36	6 57	6 81	4 78	3 98	22 8	22 0	1 74	1 40	26 5	20 6
47	1 77	40	40	5 34	5 98	4 39	3 20	21 3	28 2	1 53	1 47	28 6	24 6
387	1 64	46	46	7 58	7 74	2 38	2 12	37 9	3 4	1 58	1 20	20 8	15 5

R = recumbe d T = h d posit (h ad p) CO C rd output (l r m ut) TBV T tal bl d lume (liters) Mct M ca d pulm ry cl ul on me (seco ds) CPV Card lm blood lume (lite) by th dy m thod H Hem tocrit BSA Body rf ce rea (sq re meters)

Table IV The renal clearance of PAH (para am nohippurate) and inulin (in ml per minute) and the urinary excretion of sodium (in mEq per l ter) in 8 patients with mitral val ular disease

Case number	PAH R	PAH T	PAH Rec	I uli R	I uli T	I uli Rec	N excret on R	N excret on T	N excret on Rec
597	246	188	258	73	51	85	32	13	26
632	352	59	408	113	89	104	268	161	275
408	212	197	207	79	73	71	16	18	76
4 3	330	291	335	103	93	100	157	133	164
475	358	293	353	121	97	118	130	81	104
387	94	84	78	68	59	53	—	—	—
801	243	267	309	44	47	56	85	53	92
793	453	474	578	97	100	179	285	372	50

R Recumbent T T lt d (l d up) Rec Rec mbent af lt

Table V Statistical analysis of differences (tilted recumbent position) on blood flow blood pres (crk) and in all patients (after the addition of 2 patients with right heart failure [rhf])

	Heart rate		A V O2 difference (ml/L)		Cardiac output (L/min)	
	crk	rhf	crk	hf	crk	rhf
n_d	7	9	7	9	7	9
M_d	13 4	10 7	15 4	11 8	−0 93	−0 72
SD_d	14 7	13 9	9 27	10 8	0 58	0 65
SE_d	5 5	4 63	3 50	3 61	0 22	0 22
t	2 41	2 31	4 40	3 27	4 23	3 27
p	0 1–0 05	0 05	0 01–0 001	0 02–0 01	0 01–0 001	0 02–0 01

	B A mean		Mct (sec)		CPV/173 (L)	
	crk	rhf	crk	hf	k	hf
n_d	7	9	7	8	6	7
M_d	9 7	9 2	1 87	0 96	−0 11	−0 15
SD_d	7 80	8 93	3 20	3 92	0 23	0 24
SE_d	2 94	2 98	1 21	1 39	0 09	0 09
t	3 30	3 09	1 55	0 69	1 17	1 69
p	0 02–0 01	0 0 –0 01	0 2–0 1	0 6–0 5	0 3	0 2–0 1

motor tone is increased in small segments of the venous system during a passive tilting and it is believed that this as well as the ability to maintain central venous pressure after tilting reflect an over all increase in peripheral venous vascular tone[21,22] Tilting and the Valsalva maneuver[23] as well as positive pressure breathing[4] tend to reduce venous return and thus lower the cardiac output The resultant drop in blood pressure is partially or completely corrected for by widespread arteriolar constriction with an increase in the peripheral arterial resistance Also widespread peripheral venous constriction will lead to shifting of the blood to the central venous vessels making it available to the heart for maintaining the output[6] Thus for sustaining arterial blood pressure both arterial and venous peripheral constriction become important—the former for increasing resistance and the latter for maintaining the cardiac output

The reduction in blood flow through different areas of the circulatory system such as the kidney[14, 7] and the liver[15] in the tilted position has been amply demonstrated in man The pulmonary blood volume has been implicated as a major participant in the regional shift in blood volume Indirect evidence supports the assumption of a marked reduction in volume[6] the same applies to the few direct measurements of the intrathoracic blood volume which have been reported

The present results show that these considerations which are based on hemodynamic studies in normal individuals also are applicable to patients with mitral valvular disease inasmuch as right heart failure is absent Peripheral arterial vasoconstriction was as in normal subjects demonstrated by a decrease in the renal blood flow The finding of a concomitant fall in pulmonary blood volume and right atrial pressure indicates that the peripheral venous constriction is not extensive enough to prevent fully a shift of the blood volume On the other hand in the one patient in whom the pulmonary blood volume did not increase the right atrial pressure was also maintained

In Patient No 387 with marked congestive heart failure tilting did not produce any change in cardiac output or heart rate although the right atrial pressure

sures and renal clearances in 7 patients with mitral valvular disease without right heart failure

Stroke output (ml) crh	Stroke output (ml) hf	RA mean crh	RA mean rhf	PCV mean crh	PCV mean hf	PA mean crh	PA mean hf
7	9	5	7	7	8	7	9
−1 3	−11 8	−2 2	−2 3	−4 6	−5 5	−3 9	−4 2
12 0	12 5	2 59	2 56	4 39	4 84	6 54	6 34
4 51	4 17	1 16	0 97	1 66	1 71	2 47	2 11
3 39	2 83	1 90	2 37	2 77	3 72	1 58	1 99
0 02–0 01	0 05–0 02	0 2–0 1	0 1–0 05	0 05–0 02	0 02–0 01	0 2–0 1	0 1–0 05

CPV/TBC (%) crh	CPV/TBC (%) rhf	PAH (ml/min) crh	PAH (ml/min) hf	I nl (ml/min) crh	I nl (ml/min) hf	Na urinary excretion (mEq/L) crh	Na urinary excretion (mEq/L) hf
6	7	5	7	5	7	5	6
−1 17	−1 6	−34 0	−36 6	−17 8	−13 6	−39 4	−37 8
4 04	4 01	29 2	39 3	10 4	11 7	41 9	37 7
1 65	1 51	13 0	14 8	4 64	4 42	18 7	15 4
0 71	1 17	4 15	2 47	3 84	3 08	11	2 45
0 6–0 5	0 4–0 3	0 02–0 01	0 05	0 02–0 01	0 05–0 02	0 2–0 1	0 1–0 05

decreased somewhat This finding could be due to the presence of sustained increase in venomotor tone which prevents the shift of blood to the lower part of the body This concept is supported by the findings of Burch and Wood Litter and Wilkins[22] who demonstrated that the volume of blood contained in the peripheral system was less in patients with congestive heart failure than in individuals with a competent right heart function indicating increased venoconstriction in the former Thus in right heart failure regulatory mechanisms for maintaining the venous return are already operating in the recumbent position and counteract the pooling of blood in the upright position Similarly in studies on the effect of positive pressure breathing high mask pressure did not decrease the cardiac output in patients with congestive failure in contrast to the findings in normal individuals in whom the decrease in right heart filling pressure caused a decrease in the blood flow [24]

Cardus McKinnon and Wade made an investigation similar to the present one studying the circulatory effects of changing position in patients with mitral disease Several important differences become apparent between these two studies both in regard to technique and results They tilted the patient to 40 degrees from the horizontal and found fewer alterations than we did In their study both pulse rate and systemic blood pressure were virtually unchanged In our studies the pulse rate showed variable changes but usually increased except in those in right heart failure The reaction of the pulse is of special importance in patients with mitral disease since marked increase in pulse rate shortens the diastolic filling time to an extent necessitating a greater pressure head over the mitral valve to keep up the filling of the left ventricle This can be seen in Patient No 597 in whom the pulse rate increased from 85 to 118 per minute and the wedged pressure was unchanged although the cardiac output decreased

Another important difference is the more advanced stage of disease in the patients of Cardus and associates with initially lower blood flow—in this respect they are more nearly comparable to the patients in failure in whom no changes in blood flow were found in the present study as

The factor which gives rise to circulatory changes as the upright position is taken must be the diminished return to the right heart and the diminished pulmonary blood volume. The increase in heart rate and the decrease in systemic pulse pressure with increased mean pressure are the immediate regulatory steps taken to insure enough cerebral blood flow. The absence of those regulatory measure may be due (1) to an insufficient stimulus, (2) to the presence of congestive failure with less change in the venous return on changing position, or (3) to the modifying influence of, for example, digitalis glycosides which may keep the heart rate low, especially in patients with atrial fibrillation.

The diminished pulsations of both right atrial and pulmonary wedged pressures in the upright position, as was pointed out by Lagerlöf and Cardus[20] and associates, were also found in the present study. They probably reflect the decreased filling of the pulmonary vascular bed. As pointed out by Cardus and associates, an enlarged V wave in the wedged pressure curve cannot be used as evidence for an incompetent mitral valve. Conversely, the variation in the size of the V wave with different filling of the pulmonary vascular bed suggests that a large V wave in, for example, patients with arterial hypertension reflects increased pulmonary blood volume rather than incompetence of the mitral valve.

The diminished renal blood flow, glomerular filtration rate, and excretion of sodium in the upright position were of the same magnitudes as those seen in normal individuals. This renal vasoconstriction is probably not a specific renal reaction but signifies a part of the general systemic vasoconstriction elicited by tilting and governed by aortic-sinus caroticus reflexes. The decrease in renal blood flow seems to be of great importance—best correlated to these changes was the stroke volume—similar to what has been found under other circumstances in patients with heart disease. The patient who was tilted head down reacted with increased renal clearances and excretion of sodium, but the excretion of water changed little. Thus this reaction cannot be elicited by the intrathoracic volume receptors as suggested by Gauer and Henry.

It was obvious that the patients in this study, as in many others, had fewer respiratory difficulties in the upright position than in the horizontal. On the other hand, it is noteworthy than one patient with mitral stenosis could be tilted head down and kept in this position for 30 minutes without discomfort. The question whether the respiratory symptoms in the horizontal position depend upon the increased blood volume in the lungs or upon the increased capillary pressure with increased exudation cannot be answered, since both blood volume and pressures varied in the same direction. Probably both give rise to sensations that are of importance for the symptom of orthopnea.

Summary

1. Ten patients with mitral valvular disease were investigated in the recumbent and in the erect postures (tilted 60 degrees head up). The cardiac output, pulmonary and systemic pressures, cardiopulmonary and total blood volumes, and renal clearances of inulin and para-aminohippurate as well as the excretion of sodium were determined.

2. In 7 patients without symptoms and signs of right heart failure the cardiac and stroke outputs decreased, as well as the pulmonary capillary and the right atrial pressures. In 2 patients with clinical signs of right heart failure the cardiac and stroke outputs remained unaltered.

3. The pulmonary arterial pressure fell moderately when the patients took the erect posture. The pulmonary arterial and the systemic arterial pulse pressures were generally diminished.

4. The cardiopulmonary blood volume fell in 3 instances. This was reflected by a concomitant decrease in pulmonary capillary venous pressure.

5. The renal clearance of inulin and para-aminohippurate as well as the excretion of sodium generally decreased.

6. One patient was tilted 30 degrees head down. No symptoms appeared and no major hemodynamic change was recorded.

7. The results are discussed in view of possible hemodynamic factors that may cause orthopnea in heart disease.

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Movements of the heart during the period between the onset of relaxation and the beginning of ventricular filling

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A preceding communication dealt with the sequence of the contractile process. The present report is concerned with relaxation. The subjects, animals, and methods used were the same in the two investigations and have been considered in some detail in the previous study.[1] In brief, the normal human cardiac movements as recorded from the epigastrium, the suprasternal notch, and from numerous precordial points were analyzed in relation to the electrocardiogram and the carotid pulse (as recorded indirectly by a glycerine capsule). These motions were then compared with differentiated pressure curves as obtained from the great vessels and cardiac chambers of open-chest dogs. On the basis of such indirect evidence a hypothesis of the sequence of relaxation has been evolved.

The general schema utilized in designated movements is similar to that employed in the previous publication. The periods before and after the carotid incisural notch are called RI and RII. The abbreviation of the specific structure considered to be possibly related to or responsible for the motion is placed in parentheses and is capitalized in the case of the larger movements. Thus RI(S) refers to a large motion occurring before the incisura and thought to be due to relaxation of the interventricular septum, whereas RII (pr) indicates a small movement occurring after the incisura and believed to be dependent on relaxation of the papillary muscles of the right ventricle.

In the interpretation of the precordial traces, the directional orientation of the pickup device is significant. Records from the right and left parasternal and from the left mid-clavicular lines were obtained with the instrument pointed posteriorly. In these records a downward deflection indicates posterior movement and an upstroke signifies anterior motion. The orientation of the left axillary, suprasternal, and epigastric recordings was such that an upstroke signifies either anterior or leftward, either anterior or headward, and either anterior or footward motion in these respective regions.

Results

The observations are summarized in Fig. 1 and illustrated in the several other

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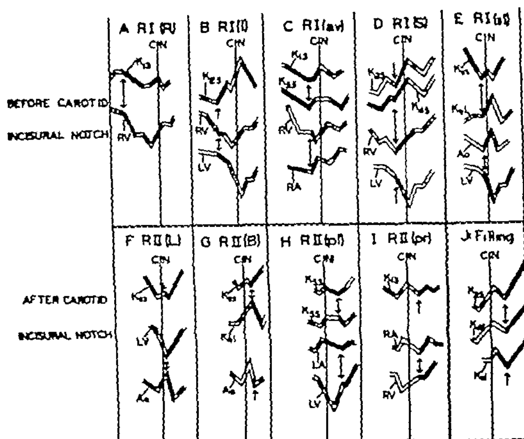


Fig 1 The diagram illu trates the motion observed bet een the onset of relaxation and the beginning of entricular filling The precordial moveme t (A) of the human subjects and the pres re elocity record from the aorta and from the cardiac chambers of the dogs are adj ted to time scale orresponding t an identical duration of rela tion in the t pecies The pecific motions are designated by the rrow and by the black areas 1 The abrupt decline in the pressure elocit trace of the right entricle (RI) ndicates the onset of relaxation of th chamber The corre ponding inward m tion in the uppe right p ternal tercostal spaces (A) is possibly due to decreasing bulge of the tricu pid leaflet B The et (harp decline the left entricular elocit record associated th decrea ing decline in the righ tr ul der at and th forward motion in the left parasternal (A) area is scribed to release of the pull f the lef tri le on the interventricular septum C The n in the right atrial eloc t t sociated h decline in the right en tricular el city record suggest that the tricu pid als moving tow ard he right trium This might be due to relaxation of papillary muscles but (see tex) ascent of the tri pid nnulu idered be mo l lel case At the same time the record f om human bject how evidence (tw d motion in both the right parasternal and left xillary area) of increase in he t ansverse diamet of he he rt D The large recip rocal motions in the t entricula elocit tra es poin toward right d m ment of he erventricular septum. The counterpart in the huma bject is large out rd deflection in the left para ternal (A) and pical (A) regions These several phenomena are scribed relaxa f the septum E The al pt rise in the aortic dens ty trace sociated th increa in t f decl ne the left ul p ur is ttributed t ascent of the aortic annulus The simultaneous outw ard m tion in the pra ter al (A) and lef epiga tric (A) regions indicates ert cal elongation of he heart F As the aortic el c it race descend sharpl there is rise (indicating decreasing te of f ll in p) in the lef entricul eloc trace These m tion nd the corresponding small decline in the sup ternal (A) trace re tt ibuted t dow d bulge of the now closed aortic cusp G Th second upstroke of the rt nd pr t nal traces ascribed o relaxation of l ngitudinal fibers hich hen contra ted exert dow nward pull on the aortic annulu The lo upstroke in the epi gastric record indicates head ard motion of the inferior border due t hange hape of the entricles the annulu ar rings ascend H nd I The several obse ed phenomena are ompat bl th relaxation of the left (pstroke in the left trial dens ty nnd upper left xillary traces sociated with dow trokes in the l ft entricul dens ty and lower left xillary ecord) nd ri ht (pstroke in the right trial elocity and parasternal traces and downstrok in the ght entri ular el city rec rd) papillary muscles J The fa outward mot in the lef precordial nd epiga tric regions and cause the beginning of passive entricula

Table I. Summary of precordial movements during relaxation

Designation (see text)		RI(R)	RI(I)	RI(ar)	RI(S)
Description		↘ k	↗ k and k_4	↗ k_1 or k_3	↗ Lower k and k_4
Number of 10 subjects showing motion		8	9	k 8 k 8	10
Time after Q (sec.)	Range	0.27–0.33	0.29–0.37	0.30–0.41	0.33–0.42
	Average	0.294	0.328	0.357	0.377
Time relation to CIN (sec.)	Range	0.09–0.16 before	0.04–0.12 before	0.02–0.13 before	0.0–0.06 before
	Average	0.114 before	0.076 before	0.047 before	0.028 before
Usual size of motion		Moderate	Small	Small	Large
Possible mechanism		Onset of RV relaxation	Release of LV tug on IV septum	Release of pull on A-V rings	Relaxation of IV septum

K_1 Right parasternal. K Left parasternal. K_3 Left mid-clavicular. K_4 Left anterior axillary. K 5 presternal. KE Epigastric.

figures. Those on the human subjects are indicated in Tables I and III and the findings in the dogs are presented in Table II.

I. Motions before the carotid incisural notch

1. INWARD MOVEMENT IN THE RIGHT PARASTERNAL REGION. Eight of the 10 normal persons displayed a downward deflection beginning at approximately 0.29 second after the onset of excitation or about 0.12 second before the carotid incisura. In some instances this was fused with the previous gradual downstroke in the same region, but in the majority of subjects this motion was distinct as a separate deflection (Figs. 1,*A* and 2,*A*). The movement, which is designated as RI(R), was largest in the upper intercostal spaces and decreased progressively in the lower regions. In patients with right ventricular hypertrophy it is markedly exaggerated in both the right and left parasternal regions, and occurs later in relation to the carotid incisura.

The pressure velocity traces from the two ventricles of the dogs usually displayed a slow decrease during late systole. The initial sharp decline occurred first in the right ventricle in some animals (Fig. 3) but not in all of them (Table II).

Comment. These observations suggest that the changes observed in the normal persons and in some of the dogs were probably related to right ventricular activity and represented the onset of relaxation in this chamber. Apparently, in the human subjects the right ventricle usually started to relax first, but in the experimental animals it appeared that either chamber might precede the other.

The larger size of the downstroke in the upper intercostal spaces to the right of the sternum would suggest that in the normal human subjects the previous bulge of the tricuspid valves was diminishing as the pressure declined in the right ventricle. A descent of the right atrial floor would be expected to be more readily reflected in the right parasternal than in the left precordial region. However, consistent evidence of a decreasing bulge of the tricuspid valve was not found in the right atrial traces of the dogs.

RI(l)	RII(L)	Terminal relaxation movements		
		RII(pl)	RII(B)	RII(pr)
↗ h and hF	↘ h ↗ hF	↗ Upper h ↘ Lower h	↗ h ↘ hF	↗ h
10	6	↗ Upper 7 ↘ Lower 7 Both 6	9	8
0 35-0 44	0 3–0 44	0 38-0 48	0 38-0 50	0 39-0 49
0 394	0 410	0 434	0 436	0 44
0 04 before 0 03 after	0 02 before 0 03 after	0 0 -0 0 after	0 0-0 07 after	0 03-0 06 after
0 009 before	0 008 after	0 033 after	0 035 after	0 043 after
Large	Small	Small	Large	Small
First ascent of aortic ring also descent of inferior border	Descent of aortic cusps	Relaxation of papillary muscles of LV	Second ascent of aortic ring also ascent of inferior border	Relaxation of papillary muscles of RV

CIN Carotid incisural notch RV Right ventricle LV Left ventricle AV Atrioventricular IV Interventricular

In the patients with right ventricular hypertrophy this inward motion is marked in the left as well as in the right parasternal region whereas the normal subjects exhibited it mainly or entirely in the latter area This finding indicates that some factor other than a bulge of the tricuspid valves is responsible for the movement in the presence of right ventricular hypertrophy As has been indicated in a previous publication[4] there is evidence for a large systolic rightward forward motion of the heart in such subjects Presumably this is reversed as the right ventricle relaxes

2 SMALL OUTWARD MOVEMENT IN THE LEFT PRECORDIAL AREA Nine of the 10 normal persons exhibited an upstroke in the traces from the h and h regions beginning about 0 03 second after the previous motion or about 0 33 second after the start of excitation and 0 08 second before the carotid incisural notch (Figs 1 *B* and 2 *B* and *C*)

Motions corresponding to this one were usually seen in the pressure velocity traces from the dogs (Table II) In most instances increasingly steep decline of the left ventricular curve was associated with decreasing slope in the right chamber An occasional animal displayed an actual upstroke in the right ventricular velocity trace as the record from the left side began its sharp decline (Fig 3 *arrow 2*)

Comment In the preceding publication indirect evidence for the presence of an initial systolic backward tug (or forward push) on the interventricular septum by the left ventricle was presented It would appear probable that the movement under discussion which is designated as RI(l) *represents the reverse of that motion* This motion was seen in most of the dogs but in both species was smaller than the similar movement [RI(S)] which occurred a little later and which is ascribed to septal relaxation If this reasoning is correct it indicates that the mural fibers relax before those in the septal and subendocardial regions

3 OUTWARD MOVEMENT IN THE RIGHT PARASTERNAL AND LEFT AXILLARY LINES Eight of 10 persons exhibited a very small outward motion in the h records (Figs 1 *C* and 2 *A* *second arrow*) and likewise

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Designation (see text)		PI(R)	RI(L)	PI(ax)	RI(S)
Description		R	↗ L and L_4	↗ L or L	↗ Lower L and L_4
Number of 10 subjects showing motion		8	9	L 8; L_4 8	10
Time after Q (sec.)	Range	0 –0 33	0 ?9–0 37	0 30–0 41	0 33–0 4
	Average	0 ?94	0 328	0 35	0 377
Time relation to CIN (sec.)	Range	0 09–0 16 before	0 04–0 12 before	0 02–0 13 before	0 0–0 06 before
	Average	0 114 before	0 0 6 before	0 047 before	0 0?8 before
Usual size of motion		Moderate	Small	Small	Large
Possible mechanism		Onset of RV relaxation	Release of LV tug on IV septum	Release of pull on AV rings	Relaxation of IV septum

R: Right parasternal. L: Left parasternal. L_3: Left mid-clavicular. L_4: Left anterior axillary. S: Suprasternal. LE: Epigastric.

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The pressure velocity traces from the two ventricles of the dogs usually displayed a slow decrease during late systole. The initial sharp decline occurred first in the right ventricle in some animals (Fig. 3) but not in all of them (Table II).

Comment. These observations suggest that the changes observed in the normal persons and in some of the dogs were probably related to right ventricular activity and represented the onset of relaxation in this chamber. Apparently, in the human subjects the right ventricle usually started to relax first, but in the experimental animals it appeared that either chamber might precede the other.

The larger size of the downstroke in the upper intercostal spaces to the right of the sternum would suggest that in the normal human subjects the previous bulge of the tricuspid valves was diminishing as the pressure declined in the right ventricle. A descent of the right atrial floor would be expected to be more readily reflected in the right parasternal than in the left precordial region. However, consistent evidence of a decreasing bulge of the tricuspid valve was not found in the right atrial traces of the dogs.

RV ↗ LV cont ued ↘	Aorta and PA ↗ LV nd RV ↘	Aorta nd PA ↘ LV nd RV ↗	RA nd LA ↗ RV nd LV ↘
14	12	12	12
13	Aorta and LV 11 PA and RV 10	Aorta and LV 12 LV and RV 8	RA 5 LV 3
0 2 6	Aorta 0 290 PA 0 305	Aorta 0 298 PA 0 310	— —
0 014 befor	Aorta 0 LV 0 015 after	Aorta 0 008 PA 0 020 after	— —
Relaxation of septum	Release of pull on semil nar rings	Descent of semilunar cu ps	Relaxation of papillary muscles
Motion usually large	Often bipha ic (see text)	Reverse motion precedes and often follow	Effect on AV cu ps usuall masked by decreasing bulge( )

AV Atri atricula

contraction of the septum These several facts and particularly the reciprocal changes in the ventricular pressures con stitute indirect evidence that these mo tions are related to relaxation of the inter *ventricular septum* which is then dis placed sharply toward the right ventricle because of the lower pressure in this chamber This movement which is desig nated RI(S) occurs at the time of the second heart sound in the aortic area *Possibly* the normal delay n the pulmonic as compared to the aortic second heart sound is somewhat related to the effect of septal displacement on the right ven tricular pressure

The apparent discrepancy between these findings and those of Rushmer who ob served only minimal displacement of the interventricular septum is probably not significant The records in the dogs are related to the rate rather than the deg ee of decline in pressure and it is probable that the magn tude of the precordial motions tends to reflect the abruptness rather than the extent of the cardiac move ment

5 OUTWARD MOVEMENT OF SUPRASTERNAL AND EPIGASTRIC REGIONS About 0 39 sec ond after the beginning of excitation and 0 01 second before the carotid incisural notch two motions were observed in all of the normal subjects These were small upward deflections in the traces from the suprasternal notch (ndic ting headward movement of the aorta) and larger up st okes *in the records from the* epigastrium (indicating footward motion of the inferior border of the heart) (Figs 1 *L* 2 *D* and *E* and 4 *C* and *D*) Since in these regions the pickup dev ce was pointed obliquely n footw rd and he dw rd d ections respectively this interpretation seems just fied

Movements which corresponded to these were observed in the dogs At the same relative time in the cycle most of them displayed a sharp decl ne n the pressure velocity trace of the left vent icle asso ciated with a rise n the record obta ned from the aorta (Fig 5 *arrow 2*) Similar findings were usually observed about 0 01 second later in the ight ventricle and pulmonary artery (Table II)

Comment The observations on the an mals showing an increased rate of decline in pressure in the ventricles asso ciated with a momentary reversal of the previous decrease in the great vessels are evidence that the semilunar rings ascending The motion is th nated RI(al) In the h

Table III Summary of normal precordial movements during ventricular contraction and

Motion during contraction				
Phase of contraction	*Motion*	*Average time after Q (sec)*	*Designation of motion*	*Phase of relaxation*
Isometric I Before onset of first heart sound	or ↗ h to h	0 03	CI(l)	Early
	Upper h ↗ Lower h	=0 01	CI(pl)	Lat
	↘ h		CI(pr)	Lat
Isometric II First heart sound to start of RV ejection	↘ hE or lower h to h ↗ h or upper h or h	0 053	CII(L)	Late
	h	0 055	CII(R)	Early
	↘ h to h	0 068	CII(S)	Early
	↘ h ↘ hE and h	0 0 8	CII(1)	Earl
	↗ Lower h	0 088	CIII(h)	—
Isometric III RV ejection to LV ejection	↘ h ↗ hE	0 091	CIII(B)	Late
	↗ h and h ↘ h	0 094	CIII( )	—

simultaneous descent of the inferior border of the heart and ascent of the aorta would suggest that the heart is elongating in its vertical dimension Apparently it represents relaxation of fibers which extend from the semilunar rings to the inferior margin of the heart

II Motions after carotid incisural notch

1 INWARD MOVEMENT IN THE SUPRASTERNAL REGION Six of the 10 subjects displayed a small downward motion in the suprasternal traces occurring approximately 0 01 sec after the carotid incisura (Figs 1 *F* and 4 *C*) Outward motion in the epigastrium which had started slightly earlier continued indicating that the inferior margin of the heart was still moving footward (Figs 2,*D* and 4,*D*)

All of the dogs (Table II) exhibited a momentary decrease in the rate of decline of pressure in the left ventricle associated with a more rapid decline in the aorta (Fig 5 *arrow 3*) Corresponding changes were frequently but not always observed in the traces from the right ventricle and pulmonary artery

Comment These findings can be ascribed to downward movement of the semilunar cusps into the ventricles as the pressure in these chambers rapidly declined The time and high frequency of these motions would make one suspect that they actually may represent heart sound vibrations However demonstration (Fig 5) that the frequency is less than that of the sounds and that the aortic and left ven

relaxation

Reverse motion during relaxation			Remarks and interpretation Contraction and relaxation of
Motion	Average time relative to CIV (sec)	Designation of motion	
↗ h to h₄	0 076 before	RI(l)	Left ventricle causing pull (↘) or push (↗) on septum
↗ Upper h ↘ Lower h₄	0 033 after	RII(pl)	Papillary muscles often masked by larger succeeding or preceding motions
↗ h	0 043 after	RII(pr)	
↘ h ↗ hE	0 008 after	RII(L)	Lower left ventricle head and displacement of blood mitral closure Bulge of aortic cusps
↘ h	0 114 before	RI(R)	Right ventricle closure and bulge of tricuspid leaflets
↗ h to h	0 0 8 before	RI(S)	Septum largest motion during contraction and relaxation
↗ h and h	0 047 before	RI(m)	Descent rings; Subepicardial fibers ( )
↗ h and hE	0 009 before	RI(al)	Descent rings; Subepicardial fibers ( )
—	—	—	Recoil of right ventricle
↗ h ↘ hE	0 03 after	RII(B)	Pull by muscles t base on semilunar ring
—	—	—	Displacement of septum to right by high LV pressure

tricular traces always display reciprocal motions makes this assumption improbable

This motion is called RII(L) in Tables I and III because it seems to be mainly due to relaxation of the left ventricle It appears to represent a continuation of the process which causes the previous movement Thus as the fibers which pass from the semilunar ring to the inferior margin begin to relax there is elongation with ascent of the semilunar rings However as the inferior border continues to descend the rapid decline in ventricular pressure allows the now closed semilunar valves to move sharply downward This in turn causes a momentary decrease in the rate of decline in pressure in the ventricles

2 TERMINAL MOVEMENTS OF RELAXATION The largest and most frequently found final motions in the human subjects consisted of a sharp downstroke in the epigastrium (Figs 1 G 2 D and 4 D) accompanied by a large outward deflection in the suprasternal traces (Figs 2 F and 4 C) At approximately the same time most of the right parasternal records exhibited outward motion (Fig 2,A) In some subjects small respective outward and inward deflections were observed in the upper and lower intercostal spaces in the left anterior axillary line (Fig 4,A and B)

The corresponding movements were sometimes but not always seen in dogs A large upstroke in the aortic velocit[illegible] was frequently observed (Fi

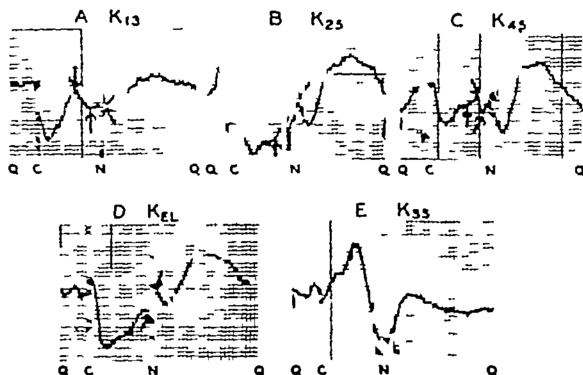


Fig I rec rdial m durin laxa D C rmal 6 ear 11 m 1 pe peed 50 mm /sec All aces tart an l end t e d tricular t tion C Car l p L ur l inci ural notch 1 The f arrow designates he low t k scribed right ricular relaxa (I I(R) The second in f ca es the ery mall up ke trial ta l t n htw rd m t t the n j l ul [RI( ) The third rrow points t he larger pstroke hi h thou ht present rela of the pap llary muscles of the ri ht entricles [RII (pr) The m t het e the sec l l third rrow ppare l are rel ted to relaxation of the interventric ular septum (upst oke and the hange hape be aort nul scend (dow trok) These two mot re larger t other are (*B* an l *C A* l C These re rd fr m the fif h tercostal pace in the left para ternal and mid-cla ular lines are similar Ea h h w ts outward m t h t nd third arrow t 0 09 and 0 03 sec before the inci ur l h (\ These m respec el trial ted to release of the backward *pull of the left en ri le [PI()) and relaxation f the in ers tr lar septum [RI(S) The* mall d wn troke indicated by the second arrow scribed o hange in hape be ring of the \ \ al ea ascend [RI( )] The later and larger dow troke fourth arr w rre pond t the large upstroke in the upra ternal notch (*E*) as the aortic annulu scend [RII(B) *D* and *F* T m tion are hos The first which start ju t before the inci ura indicates ertical elongation f he heart [I I(l)] h wn (*first rrow*) by outward deflection of the traces from the pigastrium (*D*) and from he upr ternal not h (*E*) Immediately after the inci ura the ascent of the pra ternal record becomes teeper (*E second rrow*) and the inferi border (*D second arrow*) nd the left precordial traces (*B* nd *C fourth rrow*) mo upward These several findings are scribed t release f foot ard pull on the ortic an ulu by basal fiber w th change in hape of the left entricular ca t [RII(B)]

arrow 4) but in some animals was confused with the similar movement starting earlier The right and left atrial traces occasionally displayed an upstroke at this time (Fi 3 *arrow 5*)

Comment The imultaneous occurrence of a large headward motion in both the suprasternal and the epigastric regions can be explained as follow The former movement appearing at a time when ejection has ceased and when runoff from the aorta would necessarily have the opposite effect can only be ascribed to ascent of the aortic ring The downstroke in the epigastric records indicates a change in shape of the ventricles the inferior border moves headward as the aortic valves rise These findings suggest relaxation of basilar fibers which pull the annulus downward but do not extend to the inferior border Since the deep bulbo piral muscle is made up of such fibers it seems possible that the motions in question are related to relaxation of this structure

This large movement is designated as RII(B) because it is ascribed to the fibers

at the base of the left ventricle. It should be noted that this second release of the aortic annulus differs from the one previously described [RI(al)], which is associated with footward rather than headward motion of the inferior border and is attributed to muscles which cause systolic shortening of the vertical dimension.

The other smaller and less constant terminal motions are believed possibly to be related to relaxation of papillary muscles. They are opposite in direction to the initial deflections ascribed to contraction of these muscles. Some of the dogs exhibited upstrokes in the atrial pressure velocity traces at a corresponding time in the cycle. The inconstancy of these motions in both species was probably related not only to their small magnitude but also to the effect of the declining ventricular pressure. This would tend to allow the atrioventricular cusps to sag downward whereas release of the papillary muscles would have the opposite effect. These two inconstant motions are designated as RII(pl) and RII(pr).

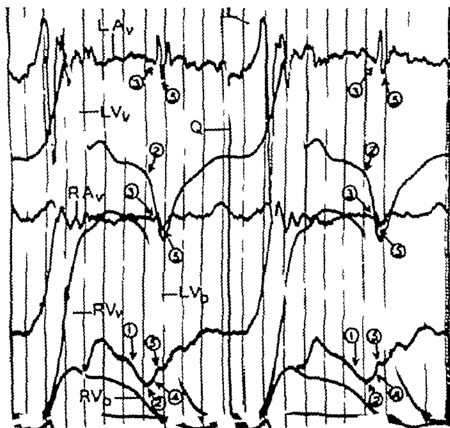
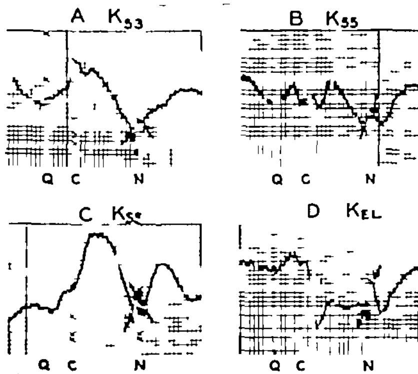


Fig. 3. Atrial and ventricular pressure velocities during relaxation. Time lines 0.04 sec. The pressure *p* and the pressure velocity curves from the four cardiac chambers are shown during two successive cycles starting and ending with the onset of ventricular excitation. The right ventricular velocity curve shows the first sharp downstroke (*1*) indicating the onset of relaxation [RI(R)]. As left ventricular relaxation starts (*2*) there is a small upstroke indicating decreased rate of fall in pressure in the curve from the right ventricle (*2*). This soon becomes more abrupt (*4*). These respective declines in the rate of drop in pressure in the right ventricle are thought to be due to release of the left ventricular pull on the septum (*2*) and relaxation of the septum (*4*). In the text these motions are designated as RI(l) and RI(S). Each atrial velocity trace shows two abrupt upstrokes. The first of these (*3*) is ascribed to release of the downward pull on the atrioventricular rings [RI(av)] and the second (*5*), which is associated with a downset in the right ventricular trace, is [illegible] related to relaxation of the papillary muscles [[illegible] and RII(pr)].



F 4 Left ventricular, suprasternal and epigastric movement during relaxation Paper speed 50 mm /sec Record start and end at onset of P of ECG Q Onset of QRS C Carotid upstroke A carotid incisural notch 1 and B Both records display small upstroke (first arrow) about 0 0 second before the carotid incisural notch This deflection designated RI( ) in the text thought to be due to increase in transverse diameter the systolic pull on the rings of the atrioventricular valves released (see Fig 2 1 second arrow) At 0 0 second after the incisural notch the K record (third intercostal space anterior axillary line) exhibits an upstroke whereas the trace taken two intercostal spaces below (B) shows downstroke (second arrow) These motions are called RII(pl) and are thought to be related to relaxation of the papillary muscles of the left ventricle They are not seen in all persons C and D The trace from the suprasternal notch (C) exhibits two upstrokes separated by smaller downstroke whereas that from the epigastrium (D) displays large outward deflection followed by inward motion indicating footward and then headward movement of the inferior border of the heart The initial upstroke in both traces is ascribed to relaxation of muscles which extend downward from the aortic annulus to the inferior margin of the heart The first effect of relaxation RI(1) of these fibers is to allow vertical elongation However because the pressure in the left ventricle is falling rapidly the now closed aortic cusp descend toward the ventricle producing the downstroke in the suprasternal trace C second arrow [RII(L)] About 0 0 second after the incisura the muscles at the base of the left ventricle appear to relax [RII(B)] allowing second and sharper ascent of the suprasternal trace At the same time change in the shape of the ventricle allows the inferior border to ascend (D second trace) Note the similarity between C and the aortic velocity trace in Fig 5

Discussion

An attempt to integrate the events during contraction with those of relaxation is illustrated in Table III Inspection of this table not only confirms the statement of Fracastorius as quoted by William Harvey [4] concerning the complexity of cardiac motion but also reveals certain gaps in the tentative conclusions

The interpretation of the sequence of events as presented is somewhat arbitrary and is based on the mean times in different persons and in different dogs Despite general broad agreement some differences

were observed Thus in the dogs relaxation sometimes seemed to begin on the left side whereas in human beings the data suggested that the right ventricle initiated the process Similarly the terminal movements ascribed to relaxation of papillary muscles although inconstant in both species were encountered less frequently in the dogs Despite the occasional disagreement the correspondence appeared to be surprisingly good when it is remembered that two different species were stud

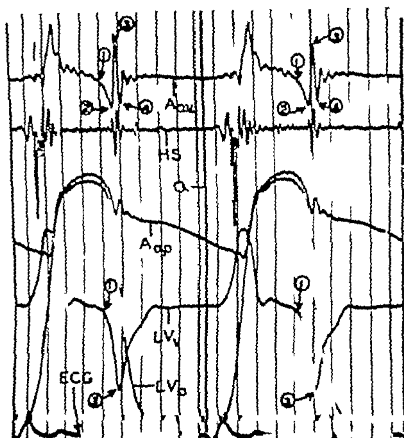


Fig 5 Left ventricular and aortic pressure velocity during elevat Time lines 0 04 sec The curves of pressure *p* and pressure velocity in the left ventricle and in the aorta are shown during two successive cycles starting and ending at *Q* The heart sounds (*HS*) as recorded directly from the left ventricular wall and the ECG are also shown The onset of the left ventricular relaxation (*1*) is shown by a sharp decline in the pressure velocity trace from this chamber and in that from the aorta While the ventricular drop is still rapid an upstroke in the aortic trace (*2*) occurs at the time of the incisura and of the second heart sound This motion which is designated as RI(vl) in the text is ascribed to the first ascent of the aortic annulus About 0 01 sec after the incisura the aortic velocity trace exhibited an abrupt downstroke (*3*) and at the same time the ventricular record displayed an upstroke indicating decreased rate of decline in pressure This movement is called RII(L) and is attributed to sudden descent of the closed aortic cusps into the left ventricle The last motion (*4*) is characterized by a rise in the aortic velocity curve This is thought to be due to a second ascent of the aortic annulus as the muscles at the base of the left ventricle relax [RII(B)] A reciprocal downstroke in the ventricular trace was seen in some of the dogs but not in this one The much higher frequency of the second heart sound and the presence of similar small deflections in the aortic pressure trace make it improbable that the deflections in the aortic velocity trace represent heart sound vibrations Note the similarity of the aortic curve to that of the human record from the suprasternal notch in Fig 4 C

ted that anesthesia was used and the chest cavity was opened in the animals and that interpretations of the velocity of change in pressure in adjacent areas of the dogs were compared with concepts derived from studies of movements of the chest wall in normal human subjects.

An ideal summary of the ventricular events would entail knowledge not only of their sequence but also of the specific muscle bundles responsible for each movement. This has been achieved only by inference, and the interpretations in Table III are based on assumptions from indirect evidence. Furthermore, it is as yet not possible to achieve a clear integration between the observed motions and the mechanical problem of the points of fixation in a bewildering syncytium of muscle fibers.

The data are in general accord with those of Rushmer, who utilized more direct techniques. Our findings support his concepts of the importance of the motions of the valve rings toward and away from the apex during contraction and relaxation, respectively.

The left ventricular outflow tract is encircled by the thick, deep bulbospiral muscle.[6] The observations on both dog and man suggest that this muscle is one of the last to contract and to relax. The mechanical advantage of such a sequence would seem obvious. Early contraction of this relatively powerful muscle would impair ejection by causing functional stenosis. There is evidence that this sometimes occurs and produces a systolic murmur and a gradient between left ventricular and aortic pressures[7] without actual structural disease of the aortic valve. It is possible that a similar mechanism in the right ventricular outflow tract is responsible for the common functional ejection murmur at the pulmonary area of healthy young persons. Late relaxation of these basilar muscles probably has the advantage of lending support for the semilunar valves during the period immediately after closure when the pressure in the great vessels is still relatively high.

The findings in Table III suggest that the respective sequences of contraction and of relaxation are as follows. Contraction appears to proceed from the papillary and subendocardial muscles to the inferior wall of the left ventricle, thence to the free wall of the right ventricle, then to the septum, and finally to the free wall and the base of the left ventricle. The relaxation sequence seems to involve successively the right ventricular wall, the outer layers of the left ventricle, the septum, the inferior margin, and finally the subendocardial and papillary muscles on both sides and the base of the left ventricle. The idea that the duration of the relaxation of the thin right ventricle is longer than that of the thicker left is surprising and calls for confirmation by more direct techniques.

Although there is still some uncertainty as to the finer details of the depolarization and repolarization processes, the evidence published by numerous investigators indicates a general correspondence between these electrical phenomena and the mechanical sequence here listed.

The data suggest that contraction spreads from subendocardial to subepicardial areas and from apex to base. Relaxation apparently proceeds from outside to inside but from apex to base. Thus the mechanical vector of relaxation would, like the repolarization vector, appear to be somewhat but not exactly opposite to the vectors of early systole. The data therefore suggest that there is a mechanical as well as an electrical ventricular gradient and that the two tend to be parallel. If this concept is correct, it follows that the electromechanical lag is of somewhat similar duration in the various portions of the ventricular muscle.

The subjects studied were deliberately chosen to represent a fairly wide age group —19 to 59. Significant age differences in the qualitative spread of contraction and of relaxation were not noted. It did appear that some motions were of larger size in the young persons and that the reverse was true of other movements. However, a larger group of subjects representing an even broader age span should be studied before an opinion is justifiable.

Finally, it should be emphasized that the conclusions here drawn concerning cardiac motion are based on indirect methods. The degree of agreement noted by the two entirely different techniques

points toward a general validity of the ideas. However, attempts are in progress to develop more direct techniques in order to subject the tentative concepts to more definitive investigation.

Summary

The sequence of ventricular relaxation as studied by indirect methods appears to be as follows:

A. Before the carotid incisural notch. (1) In some dogs and in most normal human subjects the process seems to begin in the right ventricle. (2) The onset of left ventricular relaxation is apparently associated with a small forward motion of the left precordial region. (3) As the fibers exerting a pull on the atrioventricular rings relax, the transverse diameter of the heart increases and the atrial pressures tend to rise. (4) A large forward motion of the precordium starting just before the second heart sound is probably due to relaxation with rightward displacement of the interventricular septum. At a similar time there is respective increase and decrease in the rate of *fall* in pressure in the left and right ventricles of dogs. (5) A sharp upstroke in the aortic pressure velocity curves of dogs occurs while the pressure in the left ventricle is declining rapidly. At the corresponding time the curves in human beings display evidence of vertical elongation of the heart. These several movements are attributed to relaxation of fibers which reach from the rings of the semilunar valves to the inferior cardiac border.

B. After the carotid incisural notch. (1) Soon after the preceding motion there is a descent of the closed semilunar cusps. This is shown in dogs by a decrease in the rate of fall in pressure in the ventricles associated with a downstroke of the aortic curves. In some of the records from human subjects there is a corresponding brief downstroke in the traces from the suprasternal notch. (2) The last major movement of relaxation is indicated in the dogs by a second rise in the aortic pressure velocity curve. A corresponding sharp upstroke in the suprasternal records from human subjects occurs and is regularly accompanied by a decline in the epigastric traces. This motion points toward a change in shape of the ventricular cavities as release of the basilar muscles allows a second headward rebound of the semilunar rings. It is possibly related to relaxation of the deep bulbospiral muscle. (3) Small inconstant terminal motions are thought to be the results of relaxation of papillary muscles. These movements are often masked by the opposite effects of the declining ventricular pressure with decreasing bulge of the atrioventricular cusps.

These several motions are analogous with and opposite to those observed during isometric contraction. The processes of contraction and of relaxation appear to follow sequences closely resembling those of excitation and of repolarization.

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The systemic and coronary hemodynamic effects of guanethidine*

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Although there are some reports concerning the pharmacologic action of guanethidine ([2(octahydro-1-azocinyl)-ethyl] guanidine sulfate, Ciba 5864 SU),[1-4] it seemed that additional information might be derived from a study in a larger number of animals particularly for the clarification of the action of guanethidine in acute intravenous dosage to the intact animal. Therefore the following study was made.

Material and methods

The present hemodynamic study was divided into two parts, in the first of which were 13 mongrel dogs which weighed between 15 and 28 kilograms and averaged 21.9 kilograms. Anesthesia was secured by subcutaneous administration of 3 mg. of morphine sulfate per kilogram of body weight followed in 1 hour by 0.25 ml. per kilogram of a 50/50 mixture of Dial urethane and veterinary pentobarbital.† During the ensuing 1 hour after the administration of the intravenous anesthetic, cardiac catheters were manipulated fluoroscopically into the pulmonary artery, coronary sinus, and right atrium, and a Cournand needle was placed percutaneously into the femoral artery. One hour after the anesthetic was given, cardiac output was determined by the Fick principle. Expired air was collected for a total of 5 minutes in a Tissot spirometer, and coronary blood flow was determined by the nitrous-oxide saturation method. Central venous pressure was measured by the cardiac catheter with its tip in the right atrium, whereas pulmonary arterial and systemic arterial pressures were measured, respectively, through the cardiac catheter in the pulmonary artery and the needle in the femoral artery. All pressures were recorded with Statham strain gauges and recorded on the Gilson macropolygraph.

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†Dial-urethane was furnished through the courtesy of Ciba Pharmaceutical Products, Inc., Summit, N. J., and contains 100 mg. of Dial per milliliter, 400 mg. of monoethylurea per milliliter, and 400 mg. of urethane per milliliter. Veterinary pentobarbital contains 60 mg. of pentobarbital per milliliter.

The mean pressure was determined by electrical integration of the pressure curve Cardiac rate was determined from an appropriate electrocardiographic lead Blood-oxygen and carbon-dioxide contents were determined by the Van Slyke Neill method whereas nitrous-oxide analyses were done by the method of Orcutt and Waters Oxygen and carbon-dioxide content of the expired air were determined by the method of Scholander Whole blood pH was determined with a Cambridge Model R pH meter The formulas for calculations are those generally used Work was calculated by the Starling formula of mean arterial blood pressure times cardiac output using appropriate constants and not subtracting the right or left atrial pressure The guanethidine was given as a single dose of 15 mg per kilogram of body weight intravenously through the right atrial or pulmonary arterial catheter After waiting periods which averaged 22 minutes determinations of cardiac output and coronary blood flow were repeated

In the second part of the study the response of blood pressure in the femoral artery pulmonary artery and right atrium was observed when the administration of guanethidine was preceded or followed by 5 mg of phentolamine Since it is known that the administration of reserpine produces catecholamine depletion further studies were made in a group of animals to which reserpine had been administered in a dose of 0 1 to 0 2 mg per kilogram intramuscularly for 48 hours prior to the acute administration of guanethidine in a dose of 10 to 15 mg per kilogram intravenously In the first of this group only the response of pressure to guanethidine was measured but in the latter group of 6 dogs cardiac output was measured as well by the Fick principle before and after guanethidine The details of the latter study were similar to those of the first portion of the study except that coronary blood flow was not determined and in some cases the animals were sufficiently depressed by reserpine so that the anesthetic dose was reduced

Results

Results are summarized in the Tables I II and III

Within a few seconds after administration of guanethidine there was a decrease in systemic arterial pressure accompanied generally by a transient rise in pulmonary arterial pressure and a decrease in right atrial pressure Over the next minute or so the arterial pressure tended to rise again becoming considerably elevated above the control value and accompanied by an increase in heart rate The pulmonary arterial pressure continued to remain elevated and the right atrial pressure rose slowly remaining at a higher level than it had been prior to the administration of the drug Although the arterial pressure tended to fall slowly after the initial peak the decline was sufficiently gradual so that the mean pressure was still considerably elevated during the time of the second determination of cardiac output and coronary blood flow an average of 22 minutes after the administration of the drug At the time of the second study the heart rate was increased by 43 0 per cent ($p < 0\,001$) the mean systemic arterial blood pressure was elevated 15 1 per cent ($p < 0\,001$) and the mean pulmonary arterial pressure was 42 9 per cent higher ($p < 0\,001$) Whereas right atrial pressure at the time of the second study had fallen somewhat toward the control level the mean was still variably but not significantly elevated (+ 21 9 per cent $p < 0\,1$) The minute volume of respiration did not change significantly However the oxygen consumption was increased 21 7 per cent ($p < 0\,001$) and carbon-dioxide excretion was similarly elevated (20 4 per cent $p < 0\,001$) with the body respiratory quotient unchanged The arterial hemoglobin increased 18 8 per cent ($p < 0\,001$) and the hematocrit was 22 7 per cent more ($p < 0\,001$) whereas the femoral arterial pH (−0 06 units $p < 0\,001$) and coronary sinus pH (−0 04 units $p < 0\,01$) decreased slightly but consistently As would be expected with the increase in hematocrit and hemoglobin the arterial and mixed venous oxygen content both increased significantly (11 9 and 22 6 per cent respectively) The arterio-venous oxygen difference was significantly decreased (−20 9 per cent $p < 0\,05$ Arterial and mixed venous carbon-dio[illegible] content fell significantly and the a[illegible]

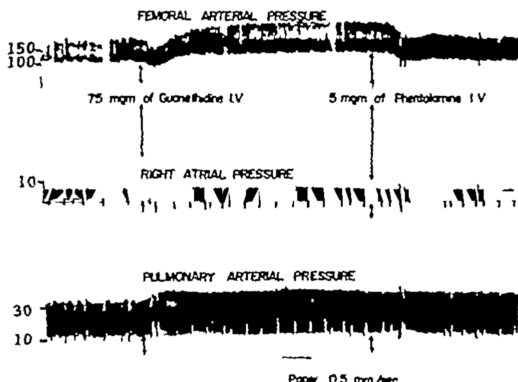


Fig. 1. The typical response of pressure to an intravenous dose of guanethidine is shown and the change in the response which followed intravenous administration of phentolamine.

venous carbon dioxide difference was significantly decreased. The coronary sinus carbon dioxide content decreased significantly (−5.1 per cent, $p < 0.01$) with the arterial-coronary sinus carbon-dioxide difference unchanged. The slight decrease in cardiac respiratory quotient was not significant.

Cardiac output increased 71.4 per cent ($p < 0.02$). The increase was quite variable from animal to animal, however, ranging from a decrease of 0.7 liter per minute in one animal to an increase to 8.1 liters per minute in another and with essentially no change in a few others. Similarly, total peripheral resistance was variable, increasing or decreasing considerably in certain cases. The over-all average of peripheral resistance decreased (26.6 per cent, $p < 0.02$), but total pulmonary resistance did not change significantly. Left ventricular work was variably but significantly increased (+106.8 per cent, $p < 0.01$) as was right ventricular work (+161.5 per cent, $p < 0.01$). Coronary blood flow increased variably (+0 to +268 per cent) but significantly ($p < 0.01$). Left ventricular oxygen consumption increased by 82.5 per cent ($p < 0.001$) and coronary vascular resistance decreased 26.7 per cent ($p < 0.01$). The index of efficiency, which relates left ventricular oxygen consumption per 100 grams per minute to left ventricular work, did not change significantly.

Phentolamine administered to the anesthetized animals immediately prior to administration of guanethidine was found to prevent the usual rise in arterial pressure. If phentolamine was administered subsequent to the guanethidine when the arterial pressure was already elevated, the pressure quickly fell to the control pre-guanethidine level, as shown in Fig. 1.

Fig. 2 reveals the fact that pretreatment with reserpine, 0.1 to 0.2 mg./Kg./day for 2 days, prevented the increase in arterial pressure which ordinarily occurs after administration of guanethidine, and Table III reveals the general hemodynamic effects of guanethidine in 6 dogs pretreated with reserpine. Mean heart rate increased while systemic mean arterial blood pressure decreased and pulmonary arterial and right

atrial pressures rose. In contrast to the untreated dogs, those pretreated with reserpine did not increase their oxygen consumption or carbon-dioxide liberation after being given guanethidine, and their cardiac output varied without a significant trend in either direction. Total peripheral resistance decreased in 5 of 6 dogs, whereas total pulmonary resistance rose in 3 and fell in 3. A rise in hemoglobin and arterial and mixed venous blood oxygen content per 100 ml. of blood, as well as an increase in hematocrit, occurred consistently after administration of guanethidine in these animals which were pretreated with reserpine.

Discussion

Clinical trials have indicated that a considerable hypotensive response may be elicited in man by guanethidine. The hypotension has been accentuated by the orthostatic position. Acute intravenous administration is reported to cause a transient hypertensive phase before the prolonged hypotensive phase ensues; indeed, the hypertensive response may be alarming. Although it has been stated that guanethidine in doses of 15 to 30 mg. per kilogram of body weight does not affect the blood pressure of normal dogs, later reports indicated that with doses of 10 to 15 mg. per kilogram intravenously an immediate hypotensive phase was followed shortly by a rise in blood pressure which was maintained for several hours. The latter reports[3] are confirmed in the present study. One example of the response to intravenous guanethidine is shown by Page and Dustan in which cardiac output increased from 2.5 to 4 liters per minute as measured by the electromagnetic flow meter. Similar

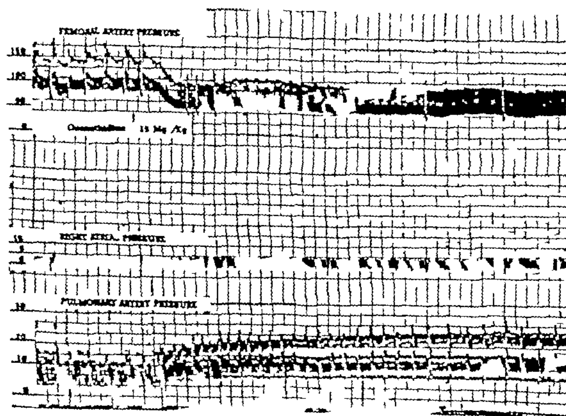


Fig. 2. A typical response of pressures shown subsequent to the administration of guanethidine to a dog which had been pretreated for 48 hours with reserpine. This response may be contrasted with the response shown in Fig. 1.

examples of increased cardiac output are found in the present series wherein the maximal increase was from 2.3 to 10.4 liters per minute. The response was, however, quite variable even though cardiac output increased in 11 of the 13 animals. The suggestion has been made that the administration of guanethidine is associated with a diminution in the available norepinephrine in the walls of the blood vessels[3] and in the heart.[11,1] Similarly, others have indicated that the first several hours after administration of Ciba 5864-SU are characterized by very transient suppression of conduction from the preganglionic to postganglionic cervical sympathetic nerves and a similar depression of vagal conduction, but of longer duration (4 hours +) followed during the first several hours after guanethidine by strong sympathetic-like actions. These are predominantly the effects which have been measured in the present study. Maxwell and associates[2] concluded that SU 5864 chronically interferes with the release and/or normal distribution subsequent to the release of the neurohumoral transmitter at the sympathetic neuromuscular junction. The presently reported fact that phentolamine may prevent or reverse the hypertensive response to guanethidine, as well as the fact that prior administration of reserpine will prevent the increase in cardiac output and the hypertensive response to acute administration of guanethidine, are both compatible with the suggestions that this phase of the action of guanethidine is due to the presence of catecholamines. Catecholamines are known to produce an increase in myocardial contractility,[4] arterial pressure, heart rate, hemoglobin concentration,[12] hematocrit, cardiac output, coronary blood flow, total body oxygen consumption, and myocardial oxygen consumption. Hence these effects may well be attributed to the release of catecholamines from peripheral sites. Additional data have recently become available which indicate that subsequent to the administration of guanethidine the catecholamine content of the ventricular wall and aorta are reduced,[11,12] and that the effect of guanethidine is different when administered to a heart-lung preparation made from a dog which has been pretreated with reserpine or guanethidine.[1] These data reveal that the inotropic effect of guanethidine disappears in catecholamine-depleted specimens and are consistent with the presently reported rise in right atrial pressure after the administration of guanethidine in dogs pretreated with reserpine.

It is unfortunate that the stability of the animal preparation used in the present study is such that only the relatively short-term action of experimental agents may be studied. Consequently, hemodynamic information was not obtained during the prolonged depressor phase of guanethidine action. Such information is highly desirable in order to complete the hemodynamic picture of this agent, and the answer is strongly suggested by the data which indicate that heart-lung preparations from dogs pretreated with guanethidine respond to additional guanethidine in a manner very similar to that of the heart-lung preparations of dogs whose catecholamines have been depleted by chronic administration of reserpine.[14] Preliminary reports in man indicate that cardiac output is unchanged or increased[7] and somewhat reduced[15] during the hypotensive phase and suggest that additional studies are needed. Renal blood flow is reported to be reduced in man subsequent to therapeutic doses of guanethidine.[15]

In the light of all information to date a working hypothesis may be that on acute intravenous administration of guanethidine there is transient sympathetic and parasympathetic blockade accompanied by transient hypotension and followed by more prolonged vagal blockade accompanied by sympathetic-like overactivity. This sympathetic-like overactivity is related to the release of catecholamines and is associated with hemodynamic effects typical of those of catecholamines. After a variable period of hours the sympathetic overactivity disappears and effects of peripheral sympathetic blockade with depletion of catecholamines become apparent. This third or prolonged hypotensive phase may last from 48 to 96 hours after administration of the drug. The response to the acute administration of guanethidine is different, therefore, in the catecholamine-depleted subject than in the normal subject.

Table I General effects of guanethidine

	Before	*After*	*% Change*	*p Value <*
Cardiac rate	79	113	+43.0	0.001
Mean arterial blood pressure	119	137	+15.1	0.001
Mean pulmonary arterial blood pressure	14	20	+42.9	0.001
Mean right atrial pressure	3.2	3.9	+21.9	0.1
Minute volume of respiration	2.6	2.9	+11.5	0.1
Oxygen consumption	115	140	+21.7	0.001
CO_2 excretion	93	11	+20.4	0.001
Body respiratory quotient	0.81	0.80	− 1.2	0.5
Arterial hemoglobin	14.4	17.1	+18.8	0.001
Arterial hematocrit	44	54	+22.7	0.001
Arterial pH	7.25	7.19	—	0.001
Coronary sinus pH	7.21	7.17	—	0.01
Arterial O_2	17.6	19.7	+11.9	0.02
Δ A V O_2	4.3	3.4	−20.9	0.05
Pulmonary arterial CO_2	52.5	48.8	− 7.0	0.001
Δ PA A CO_2	3.1	2.2	−29.0	0.02
Coronary sinus O_2	5.1	5.6	+ 9.8	0.5
Δ A CS O_2	12.3	13.9	+13.0	0.1
Coronary sinus CO_2	58.6	55.6	− 5.1	0.01

Table II Hemodynamic effects of guanethidine

	Before	*After*	*% Change*	*p Value <*
Cardiac output (L./min.)	2.8	4.8	+ 71.4	0.02
Left ventricular work (Kg.M./min.)	4.4	9.1	+106.8	0.01
Right ventricular work (Kg.M./min.)	0.5	1.4	+161.5	0.01
Total peripheral resistance (c.g.s. units)	3,733	2,741	− 26.6	0.0?
Total pulmonary resistance (c.g.s. units)	433	378	− 12.7	0.3
Coronary blood flow (ml./100 Gm./min.)	84	143	+ 70	0.01
Coronary vascular resistance (units)	1.5	1.1	− 26.7	0.01
Cardiac O_2 usage (ml./100 Gm./min.)	10.3	18.8	+ 82.5	0.001
Cardiac respiratory quotient	0.78	0.74	− 5.1	0.4
Index efficiency	0.44	0.49	+ 11.4	0.4

Table III Effects of guanethidine on 6 dogs pretreated with reserpine

	Control	*Drug*	*S.E.M. Difference*	*p Value <*
Heart rate	74	122	8.737	0.01
Mean systemic arterial blood pressure (mm. Hg)	97	82	7.388	0.1
Mean pulmonary arterial blood pressure (mm. Hg)	17	22	2.123	0.1
Mean right atrial blood pressure (mm. Hg)	2.9	4.0	0.606	0.2
Oxygen consumption (ml./min.)	100	96	9.647	0.7
Arterial oxygen (ml./100 ml.)	16.4	17.6	0.471	0.02
Arteriovenous O difference (ml./100 ml.)	4.7	4.0	0.457	0.2
Arterial hemoglobin	14.0	14.9	0.258	0.02
Arterial hematocrit	43	47	1.111	0.05
Cardiac output	2.2	2.7	0.592	0.4
Left ventricular work (Kg.M./min.)	2.8	3.1	0.632	0.6
Right ventricular work (Kg.M./min.)	0.5	0.9	0.342	0.3
Total peripheral resistance (c.g.s. units)	3,811	2,791	731.4	0.3
Total pulmonary resistance (c.g.s. units)	632	844	305.1	0.6,

Summary

1 Guanethidine was administered intravenously in a dose of 15 mg per kilogram of body weight to a series of dogs and hemodynamic studies were performed before and an average of 22 minutes after its administration

2 Subsequent to administration of guanethidine there was an increase in cardiac rate hemoglobin hematocrit and mean arterial blood pressure in the systemic arteries pulmonary artery and right atrium as well as an increase in cardiac output coronary blood flow and left ventricular oxygen consumption

3 The increase in systemic arterial blood pressure subsequent to the administration of guanethidine was blocked by immediate prior administration of phentolamine and the elevated pressure which resulted from guanethidine was reduced by the administration of phentolamine

4 Pretreatment of the dog with reserpine prevented the hypertensive phase of guanethidine action as well as the usual increase in cardiac output and body oxygen consumption

5 These results are compatible with an increased sympathetic like action during the intermediate phase of guanethidine action and suggest that this phase could be due to the release of catecholamines

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Case reports

Reticulum cell sarcoma of the heart simulating viral pericarditis

Milton Kissin M D
Robert Eisinger M D
New York N Y

Patients with malignant involvement of the heart may present w th vague constitutional symptoms intractable heart failure disturbances of rhythm coronary occlusion or pericardial effusion A recent experience with a case mimicking benign viral pericarditis prompted this report

Case report

A 79 year-old lite oman developed pain in the left houlder nteriorly and under the left breast chiefly t night The pain moved to the left shoulder posteriorly and dry cou h developed Nocturnal rise in temperature to 100 5°F as noted When she as examined tachycardia was found elec trocardiogram showed only prolongation of the Q-T interval (QT 0 45 sec) X ray examination of the chest howed marked increase in the size of the heart shadow She was referred t Beth I rael Hos pital There ere no symptom of congesti heart failure Anorexia and loss of eight were denied The patient had had no previous cardiopulmonary complaints and had enjoyed good health ll her lif except for painful osteoarthritis

On admission to Beth Israel Hospital temper ture was 100 4 F the pulse as 100 and regular and the blood pres ure as 170/80 mm Hg The pat ent as comfortable lying flat in bed nd he did not ppear to be chronically ill The neck ein ere flat Basal râles ere present which cleared hen the patient coughed The heart w lightly enlarged to percussion and the sound were di tant The second aortic sound as louder than the second pulmonic sound A Grade 1 pical systol murmur w heard The liver and pleen were not palpable there was no adenopathy nd no per pheral edema

Urinalysis was negati Hemogram revealed hemoglob 9 9 Gm erythrocytes 2 6 million leukocytes 5 400 with 71 neutrophils 24 lympho cytes 2 eosinophil and 3 monocytes Erythrocyte sedimentation rate was 80 mm in 1 hour (Wester gren) An electrocardiogram showed sinus ar rhythmia normal QRS oltage but low T w es No other abnormality was noted A roentgenogram of the chest (Fig 1) howed left pleural density nd marked cardiomegaly The pulmonary essel were not unusually prominent Fluoroscopy con firmed the impression of pericardial eff ion Pulsa tions of the cardia silhouett were minimal The esophagus was di placed posteriorly by the heart The patient was thought to h pericardial eff ion due presumabl t ural pericarditis She was treated w th antibiotics nd nalgesi s For 2 days after her admi sion the temperature rose to 101 F in the afternoon Thereafter the temper ture was normal The pain disappeared nd roentgenogram (Fig 2) revealed disappearance of the pericardial effusion

The patient went home feel ng well and remained mptomatic for 12 month Then sternal dis comfort unrelated to effort or eating ppeared Cough recurred There as no dyspnea but there w weakness and anorexia After 2 months dysp nea and pain in the right houlder developed A recurrent pericard al eff ion plus right pleural eff ion were noted The patient was given digitalis and mersalyl (hich produced con iderable diuresis) and he as readmitted to the hospital

She appeared pale and some respiratory dis tress Blood pres ure was 100/60 mm Hg pulse was 108 and regular She as afebrile There was no adenopath There ere dilated eins o er the upper nter or chest which filled from below Signs of right pleural eff ere noted The heart was enlarged to ju t beyond the left mid-cla icular line Auscultation indicated nothing remarkable A firm nontender li er as noted the edge was felt 3 cm below the costal margin The pleen was not felt There as mild pretibial edema Urinalysis hemo gram nonprotein nitrogen blood sugar and serum

F m the Departm of Medici d Pathology Beth Israel Hospital, New Y k, N Y
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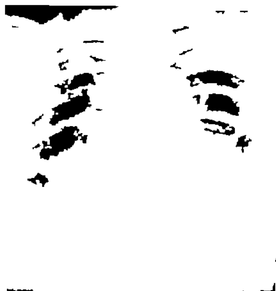


Fig 1 Original chest -ray film howing large peri cardial eff



Fig 2 Chest ra film taken 1 month after Fig 1 Pericardial eff ion ha been ab-orbed

electrolytes were now within normal limits The electrocardiogram howed an trial tachycardia and digitalis effects A chest film (Fig 3) confirmed the impression of right pleural eff ion and revealed an abnormality of the cardiac configuration The enous pressure was 170 mm of water rising t 200 mm on right upper abdominal pressure Thoracentesis yielded 200 c.c of straw-colored fluid in which no malignant cells were found Within week the patient went into coma She was treated with digitalis and mersalyl She died on the fifteenth hosp tal day

Postmortem examination done by Dr William Antopol demonstrated reticulum cell sarcoma ex ten ively involving the pericardium both tria and the left entricle with gross inv ol ement also of the mediastinal para aortic peripancreatic and mesenteric lymph nodes There was exten ion through the diaphragm and inv ion of the left l be of the liver Five hundred cubic centimeters of clear mber fluid was found in each pleural pace The pericardial space however wa obliterated by adherence of the epicardium to the involved pericardium which measured p to 3 cm in thick ness (Fig 4) The tumor filled nd obstructed the coronary nus but the enae cava were patent There w extensive necros of tumor tissue in the heart and pericardium Microscopic evidence of infiltration was noted in the gall bladder Fallopian tubes omentum and serosa of the large bowel The marrow and pleen did not contain tumor

\ d recanalized occlu ion was found 2 cm from the ori in of the right coronary artery An old calcified tuberculous complex was present in the right upper lobe

Discussion

The tenth case of reticulum cell sarcoma of the heart was reported in 1957 by Kaufman and Cohen[2] It seems unproductive to debate whether or not the heart was the primary site of tumor in the present case especially since reticulum cell sarcoma may perhaps be of multicentric origin The heart however was clearly the most extensively involved organ Prichard in his review of 150 cases of cardiac neopla ms states that fibrinous pericarditis is often associated with tumor involvement of the epicardium Other authors[4] (Grewin Barnes) also refer to pericarditis



Fig 3 One year later Recurrent pericardial effu ion right pleural effu ion and abnormal left cardiac contour



Fig. 4. Unstained myocardium at lower right. Above it, sarcoma.

complicating cardiac malignancies. We have found only one previous case, however, in which pericardial fluid due to a sarcoma subsided spontaneously, only to recur later.[4]

There is also a report of a transient pericardial effusion from pericardial metastases from a squamous cell carcinoma of the trachea, and another report of spontaneous decrease in a pericardial effusion due to pericardial mesothelioma.[4] Nabarro reported transient pericarditis with effusion in a man who died of Hodgkin's disease that involved the heart.

It is conceivable that a coincidental viral pericarditis occurred a year prior to the patient's final illness, but the coincidence would surely be astounding. It is possible, too, that some latent virus was activated by the tumor present in the heart and pericardium, comparable to the appearance of herpes zoster virus in the distribution of a nerve when the nerve root is infiltrated with lymphoma, or similar to the appearance of herpes simplex virus in a previously sensitized area under a variety of stressful stimuli. There is no evidence to support this supposition, and it is unfortunate that no viral studies were performed.

No evidence of collagen disease or rheumatic fever was noted, either clinically or at autopsy. In 1956 Dressler[14] observed pericardial and pleural effusion in patients who had suffered myocardial infarction. He noted that a similar syndrome may occur in patients after commissurotomy and believed that the condition represented a particular reaction to necrosis of the myocardium. This belief is hypothetical; the cause is not known. The facts that tumor cells were not found in the pleural fluid of our patient and that extensive necrosis was present in the tumor and in adjacent myocardium suggest that tumorous involvement of the heart may be another situation in which pericarditis and pleuritis result from cardiac damage. The old occlusion of the right coronary artery could hardly account for a postmyocardial infarction syndrome, since it was surely quite old and the sarcoma was recent and aggressive.

A clinician observing a patient with an apparently benign viral pericarditis must consider the diagnosis of cardiac neoplasm—since surgical techniques may soon be available to deal more radically with malignant disease of the heart.

Summary

A case of reticulum cell sarcoma involving the heart is reported. The presenting picture originally was that of a pericarditis with effusion, and apparently a cure was effected after a few weeks. One year later the pericardial effusion returned in association with substernal pain. Rapid death followed.



Fig. 5. Microscopic appearance of tumor.

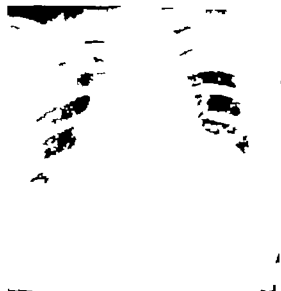


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Extracardiac influences on the electrocardiogram in organic heart disease

Observations on a patient with myocarditis

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A normal electrocardiogram by no means excludes heart disease and abnormal tracings do not necessarily indicate an abnormal heart. Special caution is needed when interpreting departure from the assumed normal of the S-T segment and the T wave. Except for the known myocardial disease states which produce S-T and T abnormalities, it is essential to realize the wide range of normal variations and the abnormalities which may be induced by extracardiac influences.[1] These latter are the position of the heart on the diaphragm (influenced by obesity, pregnancy, change in posture and respiration), the effect of drugs including nicotine, electrolyte imbalance, hyperventilation, imbalance of the autonomic nervous system, cold, fear, anxiety, fever, drinking of ice water, and meals.[2-4] The electrocardiographic changes induced by these factors revert to normal soon after the stimuli are removed, and they are often denoted as being functional in nature. The mechanism and significance of these changes are mainly obscure. It is widely assumed, however, that they are without clinical significance.

Relatively little interest has been focused on the influence of extracardiac factors on the electrocardiogram in established heart disease. The electrocardiographic changes induced in the patient reported here are similar to those characterized as functional. The evidences presented, however, are highly suggestive of organic heart disease, viz., myocarditis.

Case report

The patient was a 24-year-old military serviceman who had been previously in good health. He gave no history of rheumatic fever or dyspnea on exertion. On Oct. 11, 1959, he became acutely ill with chill, fever, and headache. During the subsequent days he developed a sore throat and general exanthema, and became jaundiced. On admission on October 17, the examination revealed a well-developed man of athletic build. He was moderately jaundiced and there was a pink maculopapular exanthema localized mainly to the trunk. His chief complaints were headache, muscular stiffness, and a sore throat which rendered peroral intake extremely difficult. Clinical signs of dehydration were present and his general condition was moderately deteriorated. The temperature was 38.2° C. The pulse was regular and 88 per minute. The blood pressure was 135/ 5 mm. Hg and remained in the same range during the illness. Clinical examination of the heart on admission gave normal findings. There was a marked bilateral necrotic tonsillitis with thick, yellow exudate and bilateral enlargement of the cervical lymph nodes. The liver and the spleen were moderately enlarged. There was no clinical sign of involvement of the central nervous system.

Laboratory findings. The hemoglobin content was 13.4 Gm. per 100 ml. The red blood cell count was 4.1 million per cubic millimeter and the white blood cell count was 13,100 per cubic millimeter. Differential blood count showed 60 to 70 per cent of the white cells to be atypical lymphocytes with large, slightly bilobed nuclei. The sedimentation rate according to Westergren was 23 mm. per 1 hour

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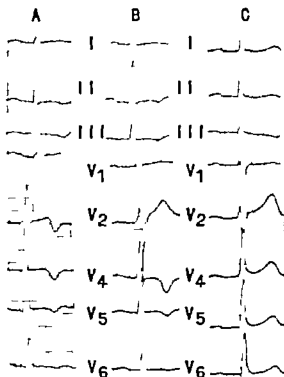


Fig. 1. The electrocardiograms obtained in the fasting state on the first (*A*), the fourth (*B*), and the twelfth (*C*) days in the hospital.

The serum bilirubin concentration was 7.3 mg. per 100 ml. The thymol turbidity test was positive. The serum level of alkaline phosphatase was 14 Bodansky units. The plasma concentration of prothrombin and proconvertin according to Owren and Aas was 62 per cent of the normal. The serum glutamic oxalacetic transaminase (SGOT) level was 120 units. Paper electrophoresis of the serum proteins was normal. The plasma creatinine concentration was 1.0 mg. per 100 ml. Three blood cultures were negative. Two throat cultures were negative for streptococci but revealed *staphylococci which were sensitive to* penicillin. The serum antibody tests for Weil and Bang diseases were negative. The serum titers of antistreptolysins and cold agglutinins were in the normal range. There was a positive heterophil antibody agglutination (Paul Bunnell test) which occurred in a dilution of 1 in 80. Urinalysis was negative except for a positive Harrison test. The spinal fluid was normal.

Diagnosis. The findings of fever, exudative tonsillitis, glandular enlargement, general exanthema, and clinical and biochemical signs of hepatic and splenic involvements were suggestive of infectious mononucleosis. The diagnosis was confirmed by the peripheral blood count and the positive Paul Bunnell test.

Course. During the first hospital week the clinical condition remained unaltered. On the tenth day in hospital there was a sudden fall in the temperature. From then on he made a rapid and complete recovery. During the next week *the sore throat cleared up* and the exanthema and the icterus disappeared. Gradually the glandular enlargement subsided and the liver and spleen could no longer be felt. Determination of SGOT was made daily. It was normal from the eleventh hospital day. The other biochemical signs of hepatic dysfunction were normalized during the following 2 weeks. The pathologic blood picture remained unaltered during his hospital stay. The patient was discharged in a good general condition 28 days after his admission. The peripheral blood smear examined 2 months later when the patient was on ambulatory control was perfectly normal.

Cardiovascular examination. On admission the pulse was regular. The blood pressure was normal by frequent measurements. No sign of congestive heart failure was present. The physical examination of the heart was normal.

Moderate clinical signs of cardiac involvement were present from the fourth to the twelfth day in hospital. Dull and remote heart sounds were observed during this period. At the apex there was a soft systolic Grade I murmur associated with a gallop rhythm. The second pulmonary sound at the base was exaggerated and reduplicated. No friction rub was observed. There was no clinical sign of pulmonary congestion. The abnormal findings by physical examination of the heart were normalized during the first few days after the temperature fell. During the acute stage as well as during the convalescent stage the roentgenologic examination of the heart was normal.

The patient has been followed regularly with clinical and electrocardiographic controls for 1½ years. There has been no symptoms or signs of heart disease.

Electrocardiographic studies. Fig. 1 shows the electrocardiograms taken with the patient in the fasting state on the first, fourth, and twelfth days after admission. In *A* and *B* of Fig. 1 there are negative T waves in the standard lead II and in the unipolar chest leads V_2-V_6. In *C* of Fig. 1 these are restored to normal. From the twelfth hospital day, i.e., 2 days after the fall in temperature, the electrocardiogram taken in the fasting state remained normal. However, for a transient period of 7 days abnormal T waves in the unipolar chest leads were inducible by *various measures. The evidences are given in* Fig. 2. Only the unipolar chest lead V_4 to V_6 are reproduced. The changes in the standard leads and in the unipolar limb leads were insignificant.

Electrocardiographic changes induced by meals and by intravenous injection of glucose. Fig. 2 *A* shows the electrocardiogram obtained when the patient was in the fasting state. This remained normal during the days on which the following studies were performed. Fig. 2 *B* shows the electrocardiogram taken 20 minutes after the patient had eaten an ordinary breakfast. Distinct T wave changes are present. Similar changes are induced by the patient ingesting 60 Gm. of glucose in 150 ml. of tap water (Fig. 2 *C*). In this case the changes appeared earlier. The electrocardiographic changes induced by meals persisted for a period of 60 to 120 minutes. Fig. 2 *D* shows the electrocardiogram 17 minutes after an intravenous injection of 40 ml. of 50 per cent glucose. The changes appeared in a few minutes after the injection and lasted for 35 minutes. The T wave changes induced

by these measures were prevented when 4 Gm of potassium chloride were ingested with a glass of water 30 minutes prior to the meal or the injection. It could also be demonstrated that the T wave changes induced by a meal or an injection of glucose were abolished in 4 to 5 minutes after an intravenous injection of 0.5 mg of dihydroergotamine.

Electrocardiographic changes induced by drugs and nicotine. Fig 2 E shows the electrocardiogram which was recorded 8 minutes after the patient had received a subcutaneous injection of 0.5 mg of Adrenalin in the fasting state. The T wave changes were at this time maximal. They lasted for 30 minutes. The changes were not preventable by peroral potassium. Fig 2 F shows the electrocardiogram 7 minutes after the patient was given an intravenous injection of 1 mg of atropine in the fasting state. Potassium did not prevent the changes from occurring. Fig 2 G shows the electrocardiogram recorded when the patient was smoking a cigarette in the fasting state. The patient was a habitual smoker. The T wave changes appeared in a couple of minutes and lasted for 5 to 10 minutes after he stopped smoking. The changes induced by nicotine were readily abolished by an intravenous injection of 0.5 mg of dihydroergotamine. They were not prevented by potassium given by mouth.

The electrocardiogram remained uninfluenced by the following: drinking of ice water, distending the stomach with effervescent powder given by mouth, the respiration phase, the posture of the body, and heavy muscular work.

These electrocardiographic changes were only inducible during the first week after the fall in temperature. Later on, the normal electrocardiogram in the fasting state remained completely uninfluenced by the above-mentioned states. For the subsequent 1½ years regularly obtained electrocardiograms re

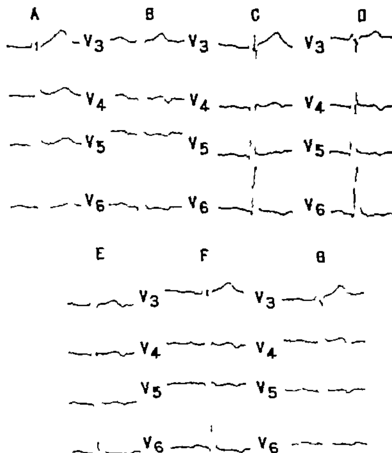


Fig 2 The electrocardiographic changes in the period from the twelfth to the eighteenth day in hospital induced by various measures. *A* Fasting state. *B* 20 minutes after breakfast. *C* 15 minutes after 60 Gm of glucose ingested in a glass of water. *D* 17 minutes after an intravenous injection of 40 ml of 50 per cent glucose. *E* 8 minutes after a subcutaneous injection of 0.5 mg of Adrenalin. *F* 7 minutes after an intravenous injection of 1 mg of atropine. *G* 5 minutes after the start of smoking.

corded under various ... perimental conditions ... cluding fever induced by typhoid ... cine has re mained normal

Discussion

The occurrence of cardiac involvement in infectious mononucleosis is well documented. This rarely will be severe enough to cause more than transient electrocardiographic abnormalities. At autopsy perivascular lymphocytic infiltration, focal interstitial collections of mononuclear cells, as well as muscular necrosis have been reported.

In the case reported upon here there were reasonable clinical, laboratory, and electrocardiographic evidences to suggest infectious mononucleosis with myocardial involvement. The nature of this process remains open for discussion. The electrocardiographic pattern during the acute phase of the illness might suggest a profound myocardial damage. Because of the associated hepatic involvement, it is impossible to reach any conclusions from the elevated SGOT level.

Transitory electrocardiographic changes induced by meals have been reported in normal individuals as well as in patients with coronary heart disease. These usually consist of S-T depressions and flattening or inversion of the T waves. Rarely are they so distinctly present as in the reported case. The nature of these changes and the explanation of their occurrence in particular subjects only are not clear. It is widely assumed that these changes are without clinical significance. It has been stated previously[3, 4] that the electrocardiographic changes induced by meals or glucose might be prevented by peroral potassium salts. It has been demonstrated here that this also might apply to the changes induced by intravenously administered glucose. This suggests that the electrocardiographic changes in some way are related to the potassium metabolism, probably to the shift of potassium from the extracellular to the intracellular myocardial space, a process which is influenced by a raised level of glucose in the blood and an increased activity of insulin. The electrocardiographic changes induced by meals and by glucose injected intravenously were readily abolished by dihydroergotamine. These findings might be explained in two ways. The effect on the electrocardiogram of meals and glucose might be related to an increased sympathetic tone which sensitizes the myocardium to the shift in potassium. Another possibility is that the shift of potassium ions is the primary mechanism which renders the myocardium especially sensitive to sympathetic influence.

It has previously been suggested that the electrocardiographic changes induced by nicotine might be related to an increased sympathetic tone.[18] The effect of dihydroergotamine during smoking, which was observed in this case, supports this view. Neither the electrocardiographic changes induced by nicotine nor those elicited by atropine and Adrenalin were preventable by peroral potassium salts. Thus there were evidences to suggest that the electrocardiographic changes induced in this case were mainly dependent on an increased sensitivity to adrenergic impulses or transmitters.

The reported electrocardiographic features are in accordance with those characterized as being functional in nature, i.e., without organic correlates and therefore without clinical significance. Electrocardiographic patterns of this kind have been ascribed to an increased sympathetic tone,[5] and individuals in whom such changes are demonstrated often present additional clinical signs of vegetative dysfunction. However, in the case presented, there were clinical and electrocardiographic evidences of myocardial involvement. This is emphasized by the fact that the electrocardiographic abnormalities were inducible only during a short transient period after the acute infectious phase. Therefore, whereas the electrocardiographic patterns denoted as functional probably are related to an increased sympathetic tone, the electrocardiographic changes in the case reported upon were presumably dependent on structural damage which increased the myocardial sensitivity to adrenergic impulses or transmitters or produced a shift of the vegetative tone of the heart in a sympatheticotonic direction.

Summary

A report is made on a 23-year-old man with infectious mononucleosis in whom

there were clinical and electrocardiographic evidences of myocardial damage during the acute phase of the illness. He made a rapid and complete recovery. During the early postinfectious phase transient electrocardiographic changes could be elicited. These consisted of inversions of the T waves in the unipolar chest leads which were inducible by various measures: an ordinary breakfast, 60 Gm. of glucose in a glass of water, hypertonic glucose given intravenously, smoking a cigarette, atropine given intravenously, and Adrenalin given subcutaneously. The changes induced by meals and glucose were preventable by potassium chloride given by mouth whereas potassium was without effect on the changes induced by other means. The electrocardiographic changes induced by meals, glucose given intravenously, and nicotine were readily abolished by an intravenous injection of dihydroergotamine. It is suggested that the transient electrocardiographic changes induced in this patient were related to structural damage, probably myocarditis, which increased the muscular sensitivity to adrenergic impulses or transmitters. It is emphasized that transient electrocardiographic changes induced by extracardiac influences which one might characterize as being functional in nature may be a sign of organic heart disease.

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The renin-angiotensin* system in hypertension

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The possibility that human hypertension could be explained on a renal basis was generally accepted after Goldblatt and associates were able to produce in the dog by partial occlusion of the renal arteries a type of hypertension the hemodynamic aspects of which are very similar to those of human hypertension.

Subsequent experiments showed that this hypertension could not be prevented by renal denervation;[2] that grafting the ischemic kidney from a renal hypertensive dog into the neck of a normal dog produces a rise in blood pressure in the recipient; that blood taken from the vein of the ischemic kidney of a hypertensive dog has higher vasoconstrictor activity than does that taken from the renal vein of a normal dog;[4] and that a renal enzyme, renin,[6] acting on a plasma globulin produces a pressor polypeptide which has been named *hypertensin*,[8] *angiotonin*,[7] or *angiotensin*.

From these experiments it became apparent that this type of hypertension was humoral and probably mediated by an increase in the renin-angiotensin system.

More than twenty years have passed and we are still wondering what the role of the renin-angiotensin system is and what are the possibilities of this being the mechanism responsible for hypertension.

Several reviews have been written on this theme, most of which seem to indicate that this humoral mechanism is responsible for at least experimental hypertension. There are other papers, however, that throw doubt on this interpretation.[1-15]

It is our purpose to evaluate some of the latest evidence for and against the renin-angiotensin hypothesis.

Hypertension may be explained by the renin theory if an increase in renin or angiotensin is found in the hypertensive animal or man, due either to an increased production or a diminished destruction. These possibilities will be discussed in relation to (a) renin and (b) angiotensin.

Renin

I. Direct evidence

A. CONTENT. The amount of renin in the kidney and in the blood has been measured in dogs before and at different intervals after partial occlusion of the renal artery. The renin content of both the blood and the kidney has been found to be increased during the first 10 days after the application of the clamp. This increase was more marked in the first week than in the second. After this period the renin content returned to normal levels. Similar results were obtained in the rabbit.[18]

In rats which developed hypertension after unilateral clipping with untouched contralateral kidney, it was found that the

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* In this article hypertensin or angiotonin will be called angiotensin, as suggested by Braun-Menéndez and Page, with the hope that this will be the standard uniform nomenclature used in the future.

renin content of the clipped kidney was either slightly lower[17] or slightly higher[19] than that of normal controls or was normal,[4] whereas the renin content of the contralateral kidney was uniformly found to be diminished.

These experiments[17, 19] suggest that the *total renin content*, if it is possible to use this term for the sum content of both kidneys, is normal or below normal. If the plasma level of renin is a representation of the level of renin in the kidney, these experiments would also be in agreement with previous findings of a decreased renin content of the plasma in hypertensive rats.[21]

Several attempts have been made in man to demonstrate an increase in the renin content in patients with essential or malignant hypertension. Initial investigations showed that the renin content of blood coming from the renal vein was not significantly different in hypertensive subjects from that in normal subjects.[22] Nor was there any difference in the renin content of the systemic blood in either group,[3] or in biopsies taken from kidneys in normal and hypertensive subjects. More recently, Peart[15] was unable to detect any traces of renin coming from the renal vein of hypertensive subjects, although his method is known to be capable of detecting this substance when the blood pressure is elevated by an infusion of renin.

Contrary to this, Haas and Goldblatt[2?] claim that renin content is increased in all periods of hypertension. They found an increase in the "total renin content" in dogs which developed hypertension when one renal artery was clamped and the contralateral one was left untouched. They also found that the renin content of the kidney of hypertensive subjects was four times greater than that of normal subjects. The method used by them is not significantly different from that employed by others, so that there appears to be no satisfactory explanation for the discrepancy in the findings.

There is much evidence, both in animals and in man, that seems to indicate that the renin content of the kidney increases whenever there is an interference with the blood flow in the kidney and/or with the perfusion pressure of the kidney. Experiments which show that the renin content of the ischemic kidney of a hypertensive dog rapidly increases when it is perfused at a normal pressure[1] are in favor of this point of view. The renin content apparently decreases again to normal levels shortly after the blood flow in the kidney or the perfusion pressure of the kidney is restored. Moreover, elevation of the perfusion pressure of an isolated kidney for 1½ to 2½ hours produced a decrease of about 43 per cent in the juxtaglomerular index,[21] which has a good correlation with renin content.

Evidence seems to indicate that the renin content or the liberation of renin is increased in the acute phase of renal hypertension, but in the chronic phase, as in essential hypertension, both content and liberation appear to be normal. Therefore, we must conclude that the experiments directed toward the investigation of renin content up to now give no support to the renin-angiotensin theory.

II. Indirect evidence

A. EFFECT OF REMOVAL OF ISCHEMIC KIDNEY. It has been well established that in dogs,[26, 27] rabbits,[27, 28] and rats with sustained experimental renal hypertension the blood pressure remains elevated after total nephrectomy until the animals die. On the contrary, in the early phase of experimental hypertension, removal of the ischemic kidney results in the normalization of the blood pressure.[27, 28]

This evidence seems to indicate that in the early period of hypertension the ischemic kidney may be releasing a pressor substance, but is against this possibility in the late phase of hypertension. This conclusion is in accordance with the results obtained by direct measurements of renin.

B. EFFECT OF ADDING A NORMAL KIDNEY. Grafting a normal kidney into a hypertensive dog,[29] rat,[30] or man[31] results in a fall in the blood pressure. It was shown that this was not due to hemodynamic artifact, since grafting a leg or creating an arteriovenous fistula does not change the blood pressure. On the contrary, the grafting of a normal kidney does not lower the blood pressure of an animal in which the pressure is elevated by an infusion of renin or angiotensin.[32] This different behavior bet... chronic hypertension and that produc...

infusion of renin or angiotensin argue against the theory that hypertension is due solely to an increase in renin or angiotensin.

C. RENIN TACHYPHYLAXIS. Repeated injections of renin bring about progressively diminishing response. This property, which is called *renin tachyphylaxis*, has been explained in various ways. The investigations seem to indicate that renin tachyphylaxis appears preferentially when the renin used is not highly purified and if the blood pressure of the animal is not allowed to return to the starting level between injections.[illegible] Hemodynamic studies have shown that the blood pressure drops without any change in the cardiac output. This indicates that during renin tachyphylaxis there is a lack of response of the arteriolar smooth muscles.

It has been shown that by continuous injection of renin it is possible to maintain a permanent elevation of the blood pressure.[illegible] Superimposed injection of renin in animals in which the blood pressure has been elevated by infusion of renin produces a drop in the blood pressure to normal levels due to the appearance of tachyphylaxis.[illegible] On the contrary, in animals with ischemic renal hypertension, after repeated injections of renin the blood pressure remains at the hypertensive level.[illegible] This difference is another argument against the possibility that experimental hypertension could be due only to a larger production of renin. Nevertheless, it has to be considered that the hemodynamic conditions in hypertension produced by continuous infusion of renin and those in hypertension due to renal ischemia are not absolutely comparable. In fact, the rise obtained by infusion is smaller than that seen in renal hypertension. Moreover, in the infused animal the response to superimposed injections of renin or angiotensin is lower,[illegible] In renal hypertensive animals it appears to be normal or increased.[illegible]

D. ANTIRENIN. The studies of Wakerling and his group,[44] which have been confirmed by others,[illegible] have shown that repeated injections of renin in dogs with acute or chronic experimental renal hypertension are followed by a drop in the blood pressure. This has been attributed to specific immunologic reactions. The possibility that this reaction could be due to a toxic nonspecific effect of the impure renin used has been suggested. Nevertheless, Wakerling was able to show that extracts of other tissues had no antihypertensive effect and that the fall in the blood pressure appeared only when antirenin titers developed.

This work in antirenin constitutes the most important argument in favor of the renin theory. However, it should be emphasized that since the renin used in these experiments was not a pure protein, it still has to be proved that similar results could be obtained with purified renin.

E. CROSS-CIRCULATION EXPERIMENTS. Isovolemic cross circulation between chronically hypertensive and normal rats[44] did not produce any change in the blood pressure of the normal rat. Such a result would not be expected if the hypertension was produced by circulating renin, since cross circulation between a rat whose blood pressure was elevated by infusion of renin and a normal rat is followed by an increase in the blood pressure of the latter. Moreover, the method was also capable of detecting renin when the cross circulation was done between a normal rat and one in which the renal blood flow was restored after a period of 4 hours of complete bilateral ischemia. Under these circumstances it has been shown that the renin content is markedly increased.

Angiotensin

1. Direct evidence

A. CONTENT. Even admitting a normal renin content, the possibility exists that angiotensin may be increased. The techniques for the measurement of angiotensin are more complicated than those used for the assay of renin, and this is probably one of the reasons why not many attempts have been made in this direction. The work of Skeggs and his group[illegible] has presented the main evidence in favor of an increase in angiotensin in experimental hypertension both in the acute and chronic phases. They also support the theory that angiotensin could be the mediator of human hypertension. In fact, Skeggs' data in malignant hypertension show an increase in angiotensin content. However, his results for essential hypertension show a great overlap with findings in a normal control group.

The method used by Skeggs and associates requires a very large volume of blood. This represents a disadvantage since bleeding per se can produce an increase in the liberation of renin. With a new method developed recently by Scornik and Paladini[44] which permits the detection of angiotensin in a small amount of blood, comparative studies of the angiotensin content of blood taken from normal and hypertensive animal have shown that there was no relationship between the amounts of angiotensin and the elevation of the blood pressure in dogs with experimental hypertension.

A critical analysis of the results does not allow one at the moment to accept an increase in the angiotensin in the blood either in the animals with experimental renal hypertension or in patients with essential hypertension. Nevertheless the difficulties in the methods must again be emphasized. Therefore additional studies are necessary before we can definitively accept or deny the existence of an increase in this pressor substance in the blood of hypertensive subjects.

II. Indirect evidence. Since the moment angiotensin was synthesized attempts have been made to compare the dynamic behavior of chronically hypertensive animal with that of animals in which the pressure was elevated by means of an infusion of angiotensin. It has to be pointed out that these conditions are not truly comparable since the situation in established hypertension must be different from that of a temporary elevation. In fact in chronic hypertension some compensatory mechanism appear such as left ventricular hypertrophy[47] or changes in the regulation of the blood pressure as for example a resetting of the carotid sinus mechanism.[48,49]

A. CROSS CIRCULATION. As previously mentioned, cross circulation between a normal rat and a chronically hypertensive one does not produce changes in the blood pressure of the normal one. On the contrary, if cross circulation is done between a rat in which the blood pressure has been elevated by infusion of angiotensin and a normal rat, an increase in the blood pressure of the latter is rapidly seen. As in the case of renin, this experiment is an argument against the possibility of the existence of a significant increase in the angiotensin content of the blood of the chronically hypertensive animals.

B. PITHING. Destruction of the central nervous system produces a drop in the blood pressure. By means of this procedure in a group of normal and hypertensive rats it was found that the blood pressure fell in both to the same level after pithing.[51] On the other hand,[4] in animals in which the blood pressure was raised by infusion of angiotensin after pithing the pressure also fell but it remained at a higher level. Interruption of the infusion produced an additional drop in the blood pressure which then reached the same level as that found in the other two groups. These experiments could also imply that angiotensin alone cannot be the cause of hypertension.

C. HEMODYNAMICS OF THE PULMONARY CIRCULATION. Early investigations[52] have shown that infusion of angiotensin elevates pulmonary arterial pressure. These have been used as an argument against the angiotensin hypothesis, since the pulmonary arterial pressure is normal in hypertensive men and animals.[53] More recently it has been shown that synthetic angiotensin in doses of 2.5 to 15 gammas produces a rise in systemic and pulmonary pressure with no change in cardiac output and with a decrease in heart rate.[54] The percentage rise in the blood pressure with this dose was equal in both circulations.

Infusion of angiotensin in normotensive men[55] produced an increase in systemic, pulmonary, and wedge pressures with no change in cardiac output. Calculation of the vascular resistance shows an elevation of the total pulmonary resistance with normal pulmonary arteriolar resistance. This suggests that the action of angiotensin takes place distal to the pulmonary arterioles, either in the pulmonary veins because of venous constriction or in the left side of the heart because of acute left ventricular failure. Recent experiments give additional support to this view. In fact, in dogs after single injections of 2 gammas per kilogram an increase in pulmonary and systemic blood pressure was found. Larger doses produced at first an increase in systemic blood pressure and subsequently an increase in

ventricular end-diastolic wedge and pulmonary pressures As soon as the systemic blood pressure dropped the left ventricular end-diastolic and wedge pressures returned to normal the pulmonary arterial pressure remained 1 or 2 mm Hg higher until the effect of angiotensin completely disappeared The same patterns were seen during infusion of 4 and 1 gammas per kilogram per minute of angiotensin [14]

In the face of these results the elevation of the pulmonary pressure produced by infusions of angiotensin appears today to be a poor argument against the angiotensin hypothesis since if there is no change in the left ventricular end diastolic pressure the blood pressure rises only a few millimeters of mercury remaining within the normal range

D ANGIOTENSINASE Several attempts have been made to see whether a difference between levels of angiotensinase (the enzyme that destroys angiotensin) in normal and hypertensive animals could explain hypertension Recent investigations showed identical results in normal and renal hypertensive rats This confirms previous experiments in dogs [17] It seems unlikely therefore that lower destruction of angiotensin due to changes in the angiotensinase content could be the cause of hypertension

Further comments

From the evidence previously presented it can be concluded that the tempting hypothesis that hypertension is due to an increase in the renin or angiotensin content is still far from being proved

Many contributions made during the last few years oppose this hypothesis Nevertheless there has to be acceptance of the fact that the methods used to measure renin and angiotensin are still unreliable and therefore the evidence in favor of or against the existence of changes in the production liberation and destruction of the substances is not conclusive

Recent studies have located the site of formation of renin in the vicinity of the glomeruli and the distal tubuli contorti in the region in which the juxtaglomerular cells are found [18] Some investigations show that the changes in renin content of the kidney under different conditions may parallel the changes observed in the juxtaglomerular cells These facts have given rise to the hypothesis that renin might be produced by these cells There is also some evidence which suggests that renin may be important in the excretion of water and electrolytes [19, 20] more so than in the maintenance of the blood pressure during the chronic stage of hypertension What is the exact role of the juxtaglomerular cells? What is the relationship between these cells and renin What are the influences of osmotic and/or pressor variations on them What is the exact role of renin in kidney function All of these questions require additional research

It seems that renin may play a role in the acute interference with blood flow and perfusion pressure in the kidney Under these circumstances renin content will increase and probably through this mechanism the pressure will be elevated But apparently other mechanisms such as changes in vascular reactivity changes in vascular structure increase in neurogenic tone etc may be responsible for the maintenance of chronic hypertension

Even if the importance of the renin angiotensin system as mediator of hypertension appears to be disputable the kidney still seems to be the place on which to focus attention in relation to chronic essential hypertension In fact ischemia of the kidney in experimental animals as well as in man is capable of producing a hypertension that is difficult to differentiate from human essential hypertension This being so it is hard to deny that angiotensin the most active pressor polypeptide known could be related to the maintenance of chronic hypertension

The final answer to what role the renin angiotensin system plays will require more investigation based on improved methods and also on a better understanding of the normal and pathologic regulation of the blood pressure

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Annotations

Isometric contraction and myocardial power

The concepts effort and work are ea ily con fused A man who keeps hea y weight up may exert himself but he delivers no work the phy ical sense *to the weight* (energy received equal force times path) Yet in the physical sense also much energy being produced by the man Compared ith the resting condition his metaboli m in creased and the energy present in chemical com pounds is converted into heat This energy is given off to the surround ngs the larger the effort the greater the amount of this dissipated energy will be

When the man actually lifts the eight over a certain height energy is delivered in both w It is delivered to the weight and in the form of heat to the surroundings The effort will depend upon both amounts of expended energy

When the left entricle in certain time ejects olume V of blood against an average pres ure p the total amount of energy deli ered by the heart muscle will likewise be = pV (ork) + d pated energy

During isometric contraction no blood i jected V = 0 and the fir t term disappears The nergy needed to bring the pres ure up to the lue which ca open the aortic valves is present in the second term it is *not* as is sometimes said equal t the product of the dia tolic pres ure in the aort nd the olume of blood the left entricle V a con sequence it is not ph ically justified to define myocardial power as the quotient of th product nd the time duration f isometric contraction

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Autoregulation of blood flow

The rate of blood flow through ascular bed tend to remain constant despite fluctuation of arterial pres ure over the approximate range of 0 t 200 mm Hg[1-4] The regulation is highly efficient in the kidney slightly less efficient in the intestine mod erately efficient in the heart and relatively ineffi cient in the limb The precise mechani m of the regu lation ha been the subject of many studies nd debates

It is clear that the mechanism reside thin the bed because regulation observed the completely isolated orga Regulation not an art fact of the method because the kidney regulates en hen untouched It also clear that the regulation result from change in the caliber of the essel rather than from change in the co ity of the blood[5] because regulation occurs during perf ion ith artificial noncellular fluids However sub ject of much debate has been whether the change in caliber passi due to change in transmural pres ure (rise or fall in t ne pres ure due t capillary filtration or also poss ubsequent t rise or fall in arterial pres ure) or activ due change in the contractile tate of ascular smooth mu the wall of the essel Those who pport he pas ive mechani m observe in association w th renal egulation large hange in ti sue pres ure as measured through large bore needl plunged int he parenchyma and large change in small enous pressure obtained by retrograde nous catheterizat on[6] These echniques accurately reflect t ue p essure and true lateral mall enou pressure in the dog forelimb but hat they reflect in the kidney ill rema unknow until the bleeding caused by the ti ue needle nd the degree of en o-venous tomoses di tal to the edge ate of the enous catheter are thoroughly in estigated Those ho support the activ mechan m find that regula tion is not soci ted with much change in the rat of flow of lymph from the kidney and that regula tion disappears after inactiv tion of ascular smooth muscle (notic death cyanides et)

There ha been an intense search for the timulus of an act response The stimul is not related to the nerve upply because regulation continues fter section of extrinsic nerves [7] blockade of ci culating techolamine and local sympa h nerves or potentiation of local parasympa

nerves Neither does t seem to be related t carbon dioxide because the kidney ontinues t regulate *after great elev tion of carbon-dioxide tension* Furthermore carbon dioxide per se seems t ha e little local vasoacti ty There is some idence *which indicates that the response might be related* t oxygen ber se th agent ppears t ha some local vasoactiv ty (nstriction when ten ion high nd dilating when tension is low) and tis ue oxygen ten ion might be expected to rise w th a increase in the rat of flow and to fall with a de crease in the rat of flow However elev tion of intraluminal pres ure by partial enous obstruction with the rate of flow held con tant produces ev dence of an active response nd in this circum stance oxygen tension does not change Further more solated small arteries and strips of mall arteries ctivel resi t distention nd extension respectivel [19,20] Hence t ppears that autoregula tion of blood flow results t lea t in part from activ change in arteriolar caliber ubsequent t some direct effect of change in transmural pres ure upon the mooth muscle ell (myogenic response) This response however might be potentiated by changes in the concentrations of vasoactiv metabolites

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Errors encountered in records of the postexercise electrocardiogram

In 1932 Wood and Wolferth fir t described changes in the postexercise electrocardiogram in patients with angina Since then the se of the electrocardiogram after exercise to determine whether at pical chest pain is due to coronary di ease and even for the early diagnosis of preclinical coronary disease ha become ncrea ingly popular especially in recent years For time t was of interest chiefly to life in urance companies nd for the evaluation of cardiac integrity in industrial medicine when the

patient might fail to reveal symptoms However as result of stati tical study by Robb Mattingly and Marks there is evidence that the test has prognostic value even with borderline or slightly positiv results This fact coupled with growing knowledge regarding the possibilities of minimizing the progress of therosclerotic heart disease is leading to the more frequent use of the postexercise electrocardiogram in routine health examinations

Approximately one third of the many postexer cise electrocardiograms sent to our Medical Depart ment are either useless or of limited alue This is due to the errors or inadequacies in the performance of the test Here are the most common errors of procedure that we ha encountered in reading record of the electrocardiogram taken after exercise

1 Taking just one series of lead immediately after exercise This is inadequate because the diag nostic changes occur frequently t period of 2 to 3 minutes or more after exercise

2 Using single test that is onl 18 to 20 trips over the steps This is frequently not enough unles the subject has substantial amount of coronary insufficiency Sometimes it is wise to do single test as precaution but if this is negativ double test mu t be done later

3 A andering base line due to loose electrode or respiratory excursions or both This makes it impos ble to measure S-T segment depres ion

4 Starting the recording too late after exercise The patient must be placed on the bed t once after exercise the cable plugged into the machine in tantly and the test tarted Fumbling around for minute or tw after exercise can result in the lo-s of a positiv response

5 Recording too many leads after exercise on one-channel machine A rate of 100 or more Lead I immediately after exercise may be seen to drop to 80 by the time Lead V is taken because a full twelve-lead electrocardiogram was leisurel taken after exercise This may result in a time lapse of 3 to 5 minutes Here again th may result in the loss of positiv response It is desirable t take Leads I II nd pos ibly III ery quickly within about 20 seconds then Leads V V and V in that order in the next 30 seconds This requires practice and team work involving t people one operating the machine nd one holding the electrodes Of course if a four-channel direct writer is vailable it is pos ible w th proper practice nd planning to take the full twelve leads after exercise but two people are still necessary to perform the test ade quately

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The cost of medical care

The cost of medical care and hospitalization com bined with the onder drugs so expens that are con tantly confronted with the problem of how to finance an operation pecially an open heart operation or long chronic illness such as subacute bacterial endocarditis or staphylococcal infection

Blue Cro and Blue Shield pay for hospital care for limited period of time but of course do noth ing to pay for outpat en or home isits The State and Regional Health Programs ponsored by the Children Bureau nd by the Department of Health pay for the major part of the cost for large number of children who are under 21 ears of age A number of labor organizations pay for the children of the w ker Nevertheless there are many other patients for hom no help vailable

When one talks with men who ha been in private practice and with the Armed Force one frequently hear that what is best bout Army medicine is tha the doctor able to giv the pa tient he care he needs Th is real challenge t the medical profes ion

Therefore when in England last fall I asked for the opportunity to discu the Briti h Health Service with some of the general practitioners The evening opened w th the comment that they did not think that the Health Serv ce was fa to the wealthy because they both paid their share of the cost of medical care and in addition had t pay the private fees and the cost of illness Th of course is true of our educational system throughout this country

The nex poi t that the doctors brought up ery emphaticall was tha the present Engli h sy tem d d not allow them ufficient time to ttend medical meetings or take refresher courses or even giv them the opportun ty for acation The doctor panels were too large to be turned over to anot

ph cian Thi their m f w a real p oblem hich need to be sol ed

The third point th t poor d ctor could make as much m od doctor Thi l o pos b u cer tem It t rere vard th bc t h eart the most The fourth poi t to be bro ht t th the doctors E land co ld w l th ir pract had previou l been the cu m cu tom hich he E gl h believed w m l t bu l g d practice int an n est t Th h er does t c ncern

A l hem g d hat l her as re govern ment t erference ith heir pr ctice the paper ark w t exces n f then ld give better car to their patient all empha zed thi a d f l len th of illnes h rter for their patien

T greate ber fit f the em wa that they ll p escribe expen drugs henc er indicated nd her l h rten the length of illnes for their patie Furthermore if he pa ient eeded h spi talization or operation he could have t Everyone empha ized the fact that the y tem permitted them to giv their patients better medical care than w t previou l pos ible

Thi not plea for the E l h health y tem but t a plea for the medical prof ion to con ider the wa and means t dev l p the be t pos ble program of medical care Blue Cross nd Blue Shield help with many illnesses but d n t cover the catastrophic illness nor the long chronic illnes of ad ancing ear Furthermore man patients who can lea t fford to pay remain w thout in urance These problem mu t be met It the duty of the medical profe on to develop the medical program hich will give everyone in our country the best pos ble medical care

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Letters to the Editor

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June 16, 1961

To the Editor:

Dr. Robert H. Bayley recently published an article in the *American Heart Journal* ("The Application of Boundary Potentials to Several Electrocardiographic Problems," 61:684, 1961) in which he quotes from a private communication from me. These quotations are incomplete and out of context and tend to give a false impression of my statements and views. The communication in question was in the form of a commentary on Dr. Bayley's paper "Unipolar Potential Measurements in the Electric Field Produced by an Arbitrary Dipole in a Circular Homogeneous Lamina" (*Circulation Research* 3:3 1959). It is also pertinent to the present article (*Comments on Bayley's paper in Circulation Research* 7:537, 1959).

BACKGROUND. Consider an arbitrary volume conductor containing electrical sources and immersed in a nonconducting fluid. There will then exist an electric potential V satisfying the following equation:

$$-g\Delta^2 V = J$$

$$g\,\Delta V\,S_+ = g\,\Delta V\,S$$

where J = electrical current source distribution, g = conductivity of medium, S = surface separating region of conductivity g from region of conductivity g'. V = unique solution to the foregoing equations exist. However, all solutions differ at most by a constant. Hence if V and V' are any two solutions, then

$$V - V' = \text{constant}$$

Every scheme for measuring the potential must consist of a series of measurements of potential difference, i.e., we must connect the voltmeter terminal to two points each time it is used. Now, if the voltmeter does not affect the potential to be measured (which can be achieved by making the voltmeter impedance much higher than the impedance between the terminals), the reading depends only on the terminal points A and B, and indeed is equal to

$$V(A) - V(B) = [V'(A) + \text{constant}] - [V'(B) + \text{constant}] = V'(A) - V'(B)$$

If this were not true, the concept of potential difference would be meaningless.

These statements are equally true if points A or B or both are located at the junction of a number of resistors whose other terminals are connected to a number of arbitrary points, provided that the resistor network does not affect the potential distribution.

Thus, each and every solution to the theoretical potential problem can be used to predict potential difference measurements. All solutions lead to the same value for potential difference. No solution is better than any other. The zero of potential is perfectly arbitrary, as any point can be used as reference and assigned the value 0.

If the electrical sources in the conductor change [with] time, then at each instant of time there exists a solution to the potential problem. This solution is exactly the one discussed above. At each instant of time, then, measurements of potential difference can be made. The potential at any point as a function of time is a meaningless concept unless we specify a reference potential. Furthermore, the time function must depend on the reference potential chosen, but it will not depend on which theoretical solution is used. Hence a statement that the potential at a point changes or does not change as the sources change is utterly devoid of meaning if no reference potential is specified.

BAYLEY'S EXPERIMENT. Bayley investigated the potential on the perimeter of a circular conductor containing a dipole source. He made measurements with respect to two references: (1) the average potential appearing around the perimeter, obtained by connecting 72 equal resistors to points equally spaced 5 degrees apart on the circumference; (2) the average of the potential on the terminal of the dipole source obtained with the use of a Wagner ground. He had previously obtained a theoretical solution for the first reference with which his experimental results checked. He did not have a theoretical solution for the second reference (which is much more difficult to obtain), but if he did, his measurements could obviously check it (by definition of solution).

What Bayley found was that for all locations of the dipole except the central one there was a difference in potential between the two references. This fact is of no practical consequence. Either set of data could lead to the same result for the potential difference between any two points on the perimeter. Bayley's experimental set-up was poor from the mechanical standpoint. He [could not] locate the dipole mechanically [...] [consis]tent with the ability to detect d[iffer]ences electrically. This fact led [...] erroneous conclusions on [...] maxima and to the fact th[...] smooth curve for [...] Wagner ground in Tab[le] [...] investigate the [...] in total potential d[...] two references [...] large in comp[...] lamina. It [...] consisting of [...] been done [...]

points It is also likely that the agreement would have been better three-dimensional model *In either case the res lts are of little more than academic nterest*

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T the Editor

Dr Da id B Geselowitz Ph D (electrical engineering) is an old hand t potent l theory Nevertheless h time w a new hand the field of electrocardiography Thirty odd years ago a pioneer in basic electrocardiography Dr Frank N Wilson (and associates) made the *bitrary* choice of *ero of potential t infinity* [or its eq *alent*] *It ppears likely that this choice was wise one* because of ts *ers ersal mathematical con enien* and because t preserves *symmetry* of the resultant dipole field I the years that followed Dr F N ilson and his co workers ntroduced *U polar Precordial Leads* which are still in wide pread use toda The ery useful nd elaborat terpretation placed pon these leads retains the basic concept of their *arbitrary* choice of *ero of potential* t *finity* [or its *quivalent*] Since Dr Geselowitz has no f ndamental disagreement w th this choice of reference potential (or any other reference choice) he might ppear to be more accommodating and go along w th electrocardiographers (physicians) or he may care t rewrit much of the last thirty years of the electrocardiographic literature For example would Dr Geselowitz prefer to choose the dipole source as zero reference and demonstrat t physicians from model that the heart field is host of *egative potential d fferences?* On the following day would Dr Geselowitz choose the dipole sink as zero reference and demon trate that the heart field is a host of *positive potential d fferences?* Ph sicians would now oscillate bet een field of *negative* potential differences and field of *positive* potential differences Perhaps a few of the most studious ph sicians might seek an a thoritati source on dipole potential theory for relief from their *le itimately created* quandry If they consult the authority Sir James Jeans (see page 27 of Reference 4) they find that h conveniently makes the choice identical t that adopted by Dr F N Wilson Later on pages 50 51 of that same work *Jeans again uses* by choice the *ero of potential* t *finity* for referenc in treating d pole potential theory Dr E Frank and Dr C Kay make this same choice m their *mathematical* treatment of dipole potential theory Generally speaking this choice for reference potential is made by ll authors of texts which I ha con lted on dipole potential theory

My difference with Dr Geselowitz centers upon h refusal to permit lectrocard ographers to retain their long estabished choice of ref rence as the *ero of potential t infinity* or t *equivalent* Academic as this may be i the higher realms of potential theory the physician *rbitrary* choice w s *made wisely* ma y years ago and for those who teach electrocardiography t physicians there is a stubborn reluctance to *alter this choic* or from *day* to *day* This position *must* appear somewhat *more tha academic* t those who in truct phy sicians n the area of electrocardiography

Technical note Excluding the electrode positions in the left hand colum colum 3 of Table 4 is that to which Dr Geselowitz letter refers Column 1 of this table gi es the *mathematically* predicted electrode position i centimeters fR(P) and column 2 gives the *mecha ically* measured distances using V_T as referenc A comparison of col mns 1 and 2 ndicates highly satisfactory *mecha ical* e lt The *distance f ult* in col mn 3 is the result of u ing the Frank Kay Wagner ground potential reference Vw In T ble 5 the obvious maximal minimal potential f ult was known to be due to a dif ference in generator output or *d pole moment* This difference is totally *important* to the argument presented The argument here is that with any dipole moment the line tegral of the potential function w th respect t V as reference is zero as it should be for an nalytic function Using V as reference the line integral is *not* *er* because the mathematical potential difference function is *ot analytic* For exa nple using the dipole source as zero reference yield group of potential differences for the boundary which are all negativ and can never pproach zero erage for any lue of the dipole moment provided this moment exi ts In the recent article the Wagner ground potential f nction is solved in terms of certa boundary potential H d E Frank and C Kay sol ed this f nction for their torso model they could ha subtracted the Wagner ground potential from their potential difference measurement nd re ed their publi hed tables[4] for correct unipolar po tentials which would ha greed with their mathematical potential function ba ed on their arbitrary choice of zero reference at infinity or its equiv lent The revised tables in their voltage maps would then be gi en an *accurate entricula center* by an accurat *ero of potential* on the *boundary*

The Geselowitz letter certainly welcome for t presents agreement with me for the first time that the E Frank and C Kay reference potential on the Wagner ground is *not equiv lent* t the *mathematical* choice of zero of potential t infinity The reference potential V_T of my a eraging net ork is *equivalent* to this choice This equivalence has now been confirmed by other investigators Therefore it is my present hope that these tw letter to the Editor will bring the potential reference problem t a final nd pleasant conclusion

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H msl de N J
April 13 1961

To the Edit r

The Edi rs l on MER 29 in the Ap l 1961 ... ue of the American H art Journal is l m t l m mly t a re e f the l y w l l l of renc held t l ... t in D mb 1959 Unfortun tely ... t represent ... th re brought f rw ...

... Wh t ... f ... d m ... precursor ... S such ev dence ... l this strictly conjecture ... Stanl ng a l ther publ h d the J l of Biological Chemistry November 1960 d not i dicate this alleged abnormal Marcos they show that MER 29 h no appreciable effect on total sterol concentr t on in t u

Next quot The remarkabl thing i that th depict on seem to occur clinically in patient w th rt rosel rotic heart dise se This has not been directly demonstr t d I agree that this h s not been demonstr t l and wonder how it can nevertheless be remarkabl Certa ly t n t demonstrated by the t o prints f the identical tracing presented in Fig 2 which are erroneou ly claimed t h c b made 6 month part

Next quot How ver studi of more than 1 year durati t the time of the Conference and more than 2 y rs now indic te that a substantial proportion f patients w th ang na pectoris im pro ... Fact are At the Conference Dr Hollander repor l definite reduction in angin l attacks in 10 out of 21 patient On the other h nd Dr H ory R ... k reported th t administr tion f MER 29 in a dosage of 250 mg d ily to total of 40 coronary patient for peri l of 3 t 5 m nth di l n t disclose e ... f cl nical or electrocardiographic improve ment Dr Halpern reported that 9 patients ut of his group of 18 show l subject e improvement of angina pectoris during MER 29 therapy but he strongly questioned whether this wa at all rel ted t a cholesterol reducing effect of the drug Finally Dr I ... speaking about group of 45 patients stated that there a a pparent improvement the symptoms but that electrocardiographic stu l g nerally show d no significant ch nge H dde l th t ... 5 t 10 y ars of study ... l be needed t det rmine the ov all prognostic sign fic nce f this drug in coronary artery dise se

In ... f these report I m puzzled ... t just what is implie l by the st t ment on p ... 433 ... the impact of the ev dence he ... ts ... nd dur t on this ... any single criterion ... Obv ... ly ... n ... f ... w ... mplet ly l cking l there ... wh Dr W lk ... at l l t the C f rer ... W must ... me that the dise se ... sence ... che ... king ... opl ... on MER 29

The manufacturers f MER 29 cla ... pl d ... merits f their pr luct They ... at ... ch ... hat h ppens t ... r ... th ... ndeq acy f the ... l ... method t ... the ... f ... ... hypothesis ...

It h uld be remembered that t th ... d th term ... gradually be ... syml ... th ... that th ... ... The long ... the ... of ... fat ... otherwise intermed ry ... the ... the end produ ... duct ... of ... sterol this intermed ry ... rol ... able for deposit where f rmerly t would ... met bolized t ... cholesterol To the un ... ind th claim that this reduces cholesterol may be ... true but everyday medical symbol ... it is highly misleading The new end product should be ... med to ... just a ... thero genic as cholesterol u ... proved otherwise Also those who cl im that no toxicity has been demon strated for the new end product (de mosterol) show

be reminded that no toxicit has been demon trated for cholesterol nthe and that thero-genicity not t ke to con ideration when di claiming toxicit

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J ly 21 1961

T the Editor

The Ed torial of April 1961 referred princi pally to the Princeton Conference because little new data from h ma being were ilable t the time of writing and also because the f nction of editorial to state an nformed pr umabl crit ical opinion t is not to be repetiti heckli t or review The editorial did *not* m represent m under tanding of ailable nformation

The question of ny the is Investigators ha looked for accumulation of sterol precursors in animal and ma treated w th triparanol none ha been found so that t more tha conjectural t as ume that the proces slowed ll along the line As made m tatement affirmatively based on 9 topic tudies in man show ng decreases in total lod terol content (cholesterol plus desmosterol) ince esffirmed and on decreases p to 50 per cent peak *total* serum terol radioactiv t fter jec tion of 2 C mev alonate[3] bsequent estimate[4] is that synthesis and delivery of radioacti sterol t the serum was 72 per cent less during treatment

this group 1 patient of 9 showed on tw occasions rise in total serum terol nd 1 showed no change while the group eraged 15 per cent decrease Others ha found ncreases in total serum sterol in 1 of 2 patients decreases averaging 10 per cent in 7 and decreases eraging 19 per cent in all of 10 patients the last cited emphasize that des-mosterol serum levels do not *rise progressively* durin treatment and infer is I had implied that the hem ical negativ feedback regulating cholesterol bio-sy thesis is lowed Hence my nference or conjec ture ha some support in dynamic studies T sue analyses in animals do not bear on this question The real question is whether the ffects observed in *most* people are enough to create a gradient from tissue to serum which will result n catabolism of *both* sterol as bile cids This is matter of opinion and experiment Some[4] belie that the response compares nfavorabl with other mea such a diet or nicotinic acid Other advocat combined treatment in some patient and suggest synergi tic or t lea t additiv action

The statement thi depletion seems to occur clinically (but) has not been directly demonstrated overcondensed and perhaps in discreet in context and lly out of it Actually in ne anal sea in treated patient howed irtually no desmosterol in coronary artery terol and hepatic total sterol (83 per cent cholesterol) of only 2 28 mg pe gram The vi thelia ma shown w re flatt at 6 months but this did not how in a head-on two-dimen ional print reduced for publication The uggestion of error is gratuitous

Anginal relief i vexed nd d fficult field Isbellus come to m nd this connection Dr Robert M Master of W R Merrell Company informs me that of July 26 1961 publication l t 134 patients w th ngina w th relief i 60 nd ECG re rsal 10 nd that his corre pondence li t nother 274 anginal patient w th 67 pe cent relief Unpublished observ tions ndicate n 58 patients w th schemic heart disease bject e relief 5 object m provement (exercise tole nce ECG) i 3 nd both n 1 The evidential loe f the l rge group m y be questioned t least the d t h m and di rection Ru sck are perhaps the mo t conv ncing to the contr ry however his 14 subjects were se lected from large array because they ga repro-ducible responses t exerci e—which most people do not—and t is conce ble that their anginal me hanisms ma be unusual some y

Lipoprotei data are sca t Paper electrophore sis[10] ndicates decrease in beta lipoproteins and beta/ lpha lipoprot in ratios most patients a review of data with Dr Mart ns show associa tion of nginal relief w th decrease beta/ lpha ratio this is under further controlled stud The manufacturers ha not stressed inadequa y of usual methods of det rmining cholest rol the presence of desmosterol largel I should think bec use they had no nformation on the effect of hyperdesmosterol emia I rabbits desmosterol is as irritating presum bly as therogenic as chole terol Los of hair and kin changes found some patients (t a severe degree 2 of our group) may be relat d to desmos terol but no one know

I summary new data ndicate unex pected side effects in some people but this is true of most drugs as they come into wide use nd does not lter the facts that this drug was first presented i usually ethical w y that it is an expedient that diminishes serum cholesterol and total serum terol in most people that t may or ma not bear on the problem of corenary therogene is and that the Editorial did not misrepresent either my understand ing of the facts ailable or fortunately those si ce accumulated

A C Corcora M D

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Book reviews

CARDIOLOGY: AN ENCYCLOPEDIA OF THE CARDIOVASCULAR SYSTEM. VOLUME 5: RELATED SPECIALTY FIELDS. Edited by Aldo A. Luisada, M.D., with foreword by Ashton Graybiel, M.D. Sponsored by the American College of Cardiology. New York, 1961, McGraw-Hill Book Company, Inc. Price $2 .50.

This is the fifth and last volume of the encyclopedia conceived by Graybiel while he was president of the American College of Cardiology and carried through by Luisada and a number of other authors. It is a miscellany of one designed to pick up loose ends. There is an element of surprise and anticipation as one leafs through it; much of the material is fascinating and most of it quite useful. The reader who must run will find it most helpful to have such a body of information collected in one spot as long as it remains reasonably current.

Part 21 (Pharmacology and the Cardiovascular System) is undoubtedly the most useful but not perhaps the most interesting section. It is for the most part authoritatively written but some of its portions, like many symposium type of articles, tend to be unnecessarily verbose. The various authors seem to make a conscious effort to provide basic therapeutic information and to avoid controversy. Even though Part 21 is hardly the place to look up such mundane items as dosages (although they are included) it constitutes a very effective monograph and some portions are outstanding. Vogl and Tabo, for example, have handled their review of diuretic agents very well; the section on digitalis (45 pages) is well organized and informative but not very readable. The section on cardiac depressant covers the ground well but seems to this reviewer to leave the implication that procaine amide is less noxious than quinidine. Quinidine is potentially a dangerous drug when employed indiscriminately, as the authors quite correctly point out. But in dealing with procaine amide (in the comparable subsection) they note that "Few side effects are generally associated with the oral administration of procaine amide in the usual therapeutic doses." Actually both drugs are dangerous if used indiscriminately and neither should be used without proper precautions. Burn's section on nicotine is interesting as is the section dealing with anesthetic agents (Part 22).

Part 24 (medicolegal, industrial, and insurance aspects) and Part 25 (stress effects) are both impressive with few reservations. Of especial interest is Rotta's very succinct account of altitude effect, and Fabricant's rather curious bit titled "World Politics and Cardiovascular Disease." Jokl's section on sports and athletics contains a large amount of information but is considerably out of date with regard to exercise physiology per se.

Part 26 will delight those old enough to have begun to wonder where cardiology came from and where it is going; others can pass on to Part 27 dealing with animal cardiology. Both parts are imaginatively done. Fishbein's short summary on cardiological bibliography is necessarily very incomplete but again points up the need for a thorough, properly annotated bibliography in the cardiovascular area. The animal section will interest those doing animal experimentation and contains information not readily available elsewhere.

In short, this is an unexpectedly interesting conglomerate of cardiological information and should be useful to practitioner and investigator alike.

Renale Hämodynamik, Wasser- und Elektrolytausscheidung bei Hypertonie. By Paul Cottier. Basle and Stuttgart, 1960, Benno Schwabe & Co. 180 pages. Price Sw. F. 15. Sol U. S. and Canadian representatives, Intercontinental Medical Book Corp., New York, N. Y. Price $4.

This book represents an impressive amount of work centered around the phenomenon of increased natruresis observed under certain conditions in hypertensive patients. The author considers that this phenomenon is a result of the elevated renal blood pressure and is independent of the factors which might play a role in the etiology of essential hypertension.

The road to this *conclusion was an arduous* one. The author studied alterations in renal function and hemodynamics in hypertensive states, diuresis and natruresis under resting conditions and after oral and parenteral fluid and sodium chloride loading, the effect of sodium chloride loading upon renal hemodynamics, the effect of changes in the extracellular fluid volume (ECV) and exchangeable sodium upon natruresis and chloruresis in hypertension, and the correlation between the rate of aldosterone secretion (measured by the urinary excretion of aldosterone) and natruresis. He also attempted to correlate the grade of hypertension with the degree of pathologic changes in the target organ.

Many studies of this type have been reported previously. However, in an area as confused by contradictory reports as this one, repetition is necessary. What disturbs the reviewer is that by focusing perhaps too sharply on one aspect of the problem the author appears to lose his perspective at times. In some of his studies he uses mathematical medium arterial pressure

$$\frac{\text{systolic} \quad \text{diastolic}}{2}$$

erroneously referred to as "mean arterial pressure" in the English summary, as a measure for grading the severity of hypertension. Unfortunately, this formula, which has also been used by others, would place a patient with a blood pressure of 180/120 mm. Hg in the same category as one with 210/90 mm. Hg. One wonders whether this makes much difference to the author. Indeed, in some chapters he creates the impression that he doubts the basic difference

between essential hyperten ion and an elevation of systolic blood pressure in arteriosclerosis. His caution expressing himself on this and on some other subjects amounts t ambiguity. At the same time he is quite unequivocal in stating that the rations in the ECV in the exchangeable sodium and in the aldosterone secretion ha been ruled out pos ible factors in the h pertension. This an overstatement. The ell documented findings of Gamble of Stra and co-workers Bartter nd co-workers Crawford and Ledermann and more recentl of Bald m and associates do not appear t ha been di proved by the author studies. Nor does the author purely speculative theory of fluctu ting renal vasospasm replace the concept of H W Smith in explaini g the time lag phenomen n of sodium excretion.

Thi work clarified some hitherto blurred detail m th field and that is contribution. The book does not produce new facts of basic importance but the sheer ma of data accumu lated in it and the exten n discus ion of the findings of others make this olume usef l for students of hyperten ion and electrol te metabolism. The chapter in which report is made on comparativ study of the effect of prolonged hypoten therapy with ingle drug (reserpine hydralazine chlorothiazide mecamylamine) will be of interest to clinicians.

EINFUHRUNG IN DIE PHYSIOLOGIE DES MENSCHEN (I troduction t the Physiology of Man) By Hermann Rein 13th and 14th revised editions issued by Max Schneider Professor der Physiologie, Direktor des I stituts fur Normale und Pathologische Physiologie der Universitat Kol Berlin 1960 Springer Verlag 493 illustrations 765 pages Price DM 59 60

The textbook of phy iology by Hermann Rei had had 10 editions before the death of the author After that it wa issued by his pupil Max Schneider. Comparing the recent thirteenth and fourteenth edition ith the former ones the reader readil aware of the great increase in knowledge in the field of physiology that has been attained during the past 10 years I p te of the olumi nous increase of facts Schneider has been successful in maintaining the ba ic concepts of h teacher. The special aim of the book is to present scientific interpretations for the phy iologic facts of life and to provide understanding for their terrelationsh p For this purpose great number of ingle facts are described on a broad scale to reveal the phy iolog t method of combination and correlation of phy iologic events. The part concerning the heart and peripheral circulation is described in detail because of ts great importance to the practitioner. Here the cardiol gist will find all the interesting physiologic reaction of stimulation of the heart in nervation of the heart cardiac dynamics changes of shape of the heart during contraction of the heart val e-systems nd of energy metabol m— all these facts are presented according to the latest knowledge. The cardiol gist will al-o be terested in the description of the peripheral circulation in renal physiology and in fluid and electrol te metaboli m these too are presented in the most modern pects. All in all this is a textbook which reveals the newest platform of scientific knowledge in physiology and t is presented in an excellent and comprehen ive manner.

CARDIAC PROBLEMS Edited by K. Shirley Smith B.S.C. M.D. F.R.C.P. Physicia nd Cardiologist t the Charing Cross and London Chest Hospital with the aid of sixteen contributors. Papers read at three symposia. Part I Symposium held Dec 6 19 7 Part II Symposium held July 15 1959 Part III Symposium held June 8 1960. The Che t and Heart Association, Ta istock House North T istock Square London England London 1961 W terlow & Sons Ltd 144 pages Price $3 50

The papers presented in this small volume were originally given by a group of British cardiologists at three symposia held in 19 1959 and 1960 Revised and brought p to date these papers cover wide range of subjects in heart disease including cardiopulmonary d ease heart failure hypertension the surgical treatment of heart disease and the management of coronary disease. The emphasis primaril on clinical a pects of disease although phy iologic mechani m are frequen ly in oked t further understanding.

I general the papers strike note of excellence and brevity and they will be of interest to most students of heart d ease. Although the emphasis on the t treatm of physiologic mechani ms primarily for the recognition and management of clinical problem may be somewhat heretical in the eyes of some American readers the di rectness and simplicity of these papers is refreshing. Of particular interest is the chapter on endocrine aspects of heart failure although pos ibly overly implified it is stimulating and provocative.

Announcements

AN INTERNATIONAL RESEARCH CONFERENCE ON FAT AS A TISSUE will be held on Thursday and Friday, Nov. 1 and 2, 1962, at the Lankenau Hospital, Philadelphia 31, P.

A MEDICAL CONTINUATION COURSE, Intermediate Electrocardiography for General Physicians and Specialists, is to be presented at the Center for Continuation Study, University of Minnesota, Minneapolis, Minn., on Jan. 2-6, 1962.

For further information concerning this course, write to the Director, Department of Continuation Medical Education, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minn.

SPECIAL PROGRAM FOR RESEARCH GRANTS IN RADIOLOGICAL HEALTH. In view of the rapid expansion which is forecast in the use of nuclear energy, x-ray, and other sources of radiation, a greatly expanded program for research grants in the field of radiological health has been developed. The grants are offered to support research by individual university, hospital, laboratories, and other public or private institutions in the assessment and control of man-made and natural radiation exposures to the individual, no matter how the separate components may originate. The knowledge and skills of many professional disciplines and specialties—physicians, engineers, physicists, chemists, educators, statisticians among them—are needed to find answers to the many challenging questions in radiological health.

Research proposals should contribute to the determination of the extent and character of the radiation problem as well as the mechanisms by which radiation produces damage. Studies aimed at the elucidation of the radiation damage cause and effect relationship are essential if low level and long term radiation exposure effects are to be accurately assessed and general control programs organized. Therefore, basic studies relating to critical body organs and systems, preferred metabolic pathways for specific radioactive contaminants, and an understanding of the radiosensitizing and modifying effect of various materials are encouraged.

Broad epidemiological studies aimed at a scientific evaluation of the long term effects, such as aging, congenital malformations, genetic effects, behavioral patterns, and induction of cancer, are also of primary concern. Field studies of the movement of radioactive contaminants in biota and human food chains are of special interest since it is known that the physical environment may be greatly altered by biological activity, as for example, the concentration of water borne radionuclides in micro-organisms and fish.

Purely physical studies, such as chemical mechanisms in radiation chemistry, the design of equipment, and the development of techniques to accurately assess or reduce the population dosages are mandatory for a successful research program.

Studies aimed at directing scientific findings toward control devices or procedures are necessary.

A total view of man's ecological system as are studies that attempt to assess the relationship between health hazards created and possible benefit derived by radiation usage. The determination of the consequences of radiation exposure for present and future generations will require intensive investigation.

For information and/or application forms, write to Dr. Paul F. Hahn, Chief, Office of Extramural Grants, Division of Radiological Health, U. S. Public Health Service, U. S. Department of Health, Education and Welfare, Washington 25, D. C.

REPORT ON POSTGRADUATE PHYSICIAN EDUCATION. A report on the status and aims of postgraduate medical education, planned to serve as a guide to future activities in this field, has just been published by the American Heart Association. Entitled The Physician: Continuing Education, the report was prepared on behalf of the Association Committee on Professional Education by a group of 13 volunteer physicians headed by Dr. Stewart G. Wolf, Oklahoma City, Okla.

According to the report, an analysis of current activity in the field of postgraduate medical education indicates that present techniques reach relatively few physicians. It notes that training programs have not always been adapted to the needs of practicing physicians.

The report discusses various educational techniques for postgraduate or continuing education in terms of their relative merits and emphasizes the need for research to develop new training methods as well as to improve evaluation of those now currently used. It concludes with recommendations for a new and vigorous approach to the problem by the Association and its affiliates, outlining a number of pilot projects which will involve participation by affiliated Heart Associations on a selective basis. The ultimate goal of the pilot studies is to improve medical care for patients with cardiovascular disease.

Copies of the report, a 48-page paper-bound volume, may be obtained from local or state Heart Associations or through the American Heart Association, 44 East 23rd Street, New York 10, N. Y., at 60 cents per copy.

American Heart Journal

November 1961 Volume 62 Number 5

Obituary

Gustav Nylin

1892-1961

By Gunnar Biorck, Stockholm, Sweden

Professor Gustav Nylin of Stockholm died August 6, 1961, from cardiac infarction. He was born in 1892. Next of kin are his wife Ingrid, two daughters, and grandchildren.

With the passing away of Gustav Nylin Swedish medicine has lost one of its internationally most prominent personages.

What Gustav Nylin achieved as a physician depended largely on his genuine appreciation of scientific research. His career was unusual: as a practitioner and school physician he became interested in the physical development of school children, and he presented his thorough observations in this field in the form of a doctor's dissertation. This important work opened the doors of the Iacobaeus Department of Medicine at the Serafimer Hospital, where he had the opportunity to put into practice and further develop his views on the problems of the physiology of the heart and circulation.

Contrary to more old-fashioned conceptions hampered overmuch by pathological anatomical ideologies, Gustav Nylin considered it essential to study scientifically heart function in living man with the aids of modern medicine. At an early stage he devised a test for heart function and together with Liljestrand and Lysholm developed a method for a quantitative study of the heart roentgenologically. This work awakened his subsequent interest in blood volume conditions in different diseases of the circulation. The



Professor Gustav Nylin, 1892-1961

medical use of radioactive isotopes opened up an entirely new approach to these problems, and in cooperation with de Hevesy he became a pioneer within a field of research which later became universal.

During the last years the circulation of the brain especially caught his interest, and to the very last, aided by American funds, Gustav Nylin worked actively in this field of research in the laboratory which the city of Stockholm placed at his disposal when he retired from his position as head physician at the South Hospital in Stockholm.

Gustav Nylin gave only a short period of his life to the Serafimer Hospital. He subsequently became head physician at Sabbatsbergs Hospital and thereafter at the cardiac department of the South Hospital. He had a burning passion for research and conveyed this attitude also to his co-workers. As the years went by, more and more foreign physicians and research workers visited his department.

Because of his undaunted activity and devotion to cardiology, Gustav Nylin played a prominent part as an organizer both at home and internationally. He became the first chairman of the Swedish Cardiological Society and also presided over the Second European Congress in Stockholm, 1956, as chairman of the European Cardiological Society. He was a member of several scientific societies abroad and was often asked to lecture the world over.

Gustav Nylin was an enthusiastic person and a faithful friend who was always ready to help his fellows and his patients. Despite success he remained simple and unassuming in his ways.

Swedish cardiology of today is to a great extent based on the work of Gustav Nylin and on the impulses he has given. He will be sadly missed by many cardiologists all over the world who are indebted to him for all the knowledge, encouragement, and support he has given.

Editorials

Concentrating mechanism of the kidney from a comparative viewpoint

Bodil Schmidt-Nielsen
Durham, N. C.

The mechanism for making a urine that is osmotically more concentrated than the blood is found in three groups of animals only: the insects, the birds, and the mammals. Thus one might say, is reasonable. All three groups are terrestrial, and consequently the conservation of water is essential. In an early stage of evolution the ability to make a urine that was more concentrated than the blood must have become part of the adaptation to a terrestrial habitat.

This, however, is an oversimplification. There are other groups of animals which are also terrestrial but which do not possess kidneys that can produce a concentrated urine. Furthermore, a marine animal like the fish is also faced with a need for the conservation of water and the excretion of salt, and yet its kidneys are only capable of producing a urine that is almost isotonic with the blood but never hypertonic.

Thus the ability to concentrate the urine was not an essential feature of water conservation but came about as a rather special adaptation. In the insects the mechanism through which a concentrated urine is formed is [illegible] different from that of birds and mammals. The insect kidney, the Malpighian tubules, also h[illegible] an origin different from that of all other kidneys in the animal kingdom. The Malpighian tubules start as an outgrowth from the intestine and probably originate from the endoderm. In all other animals, invertebrates as well as vertebrates, the kidney is derived either from the ectoderm, ectoderm and mesoderm, or mesoderm alone.

In the following I will attempt to show that all kidneys (except the insect kidney) basically operate in a similar manner in handling salt and water along the tubule, but that the bird and, to a greater degree, the mammalian kidney through ingenious engineering can produce a urine that is more concentrated than the blood.

Let us begin with a quite primitive kidney, the nephridium of an earthworm (Fig. 1 *A*). An earthworm l[illegible] in a moist environment is essentially a fresh-water animal. The osmotic concentration of the body fluids of the earthworm is about two thirds of that of mammals. Water is taken up by osmosis, and consequently there is a need for the excretion of water with conservation of salt, i.e., the excretion of a urine that is highly hyposmotic to the blood.

The functional parts of the nephridium are roughly similar to those of the mammalian renal tubule: nephridiostome corresponding to the glomerulus, a proximal and a distal tubule. Ramsay performed micropunctures on the nephridium and found that in the proximal tubule the osmolality of the tubular fluid *remains* identical with that of the coelomic fluid

[illegible] D[illegible] N. C.
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*Th[illegible] supported [illegible] from the American Heart Associ[illegible]

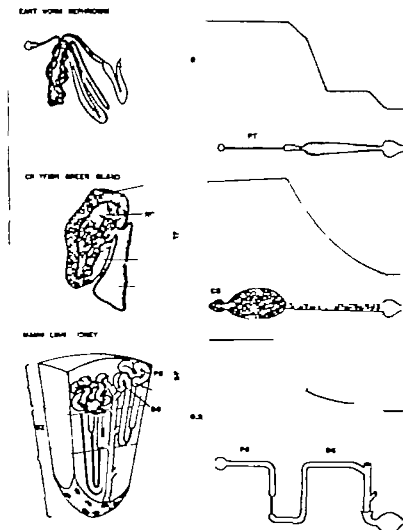


Fig 1 The osmotic concentration along the excretory tubule of the earthworm the crayfish and the mammal *A Earthworm nephridium* *PT* proximal tubule *DT* distal tubule *B* bladder Ramsay data are presented in the graph The osmotic concentration in the tubular fluid divided by the osmotic concentration of the body fluid are plotted against the site of the puncture on the nephridium. *B Crayfish green gland* The drawing has been copied from Peters *CS* coelomic sack *L* labyrinth *NC* nephridial canal *B* bladder Peters determinations of the chloride concentration in the various parts of the green gland are presented as the ratio between the concentration in tubular fluid and the concentration in the body fluid *C Mammalian kidney* *G* glomerulo *PC* proximal convolutions *DC* distal convolutions *C* cortex *M* medulla *OZ* outer zone of the medulla *IZ* inner zone of the medulla. Along the ordinate are given the osmotic concentrations in the tubular fluid divided by the concentration in the blood. The solid line represents the data obtained by Wirz[4] from rats producing a hypotonic urine. The dotted line represents data obtained in rats during low diuresis when the urine was hypertonic (Wirz[4] and Gottschalk and Mylle[5])

whereas in the distal tubule the osmolality drops sharply (Fig 1,A)

A similar finding has been reported by Peters in another fresh water animal the crayfish The crayfish kidney the green gland is situated in the head of the animal and the bladders open to the outside through the operculae near the antennae (Fig 1,B) In the coelomic sack that functionally corresponds to the glomerulus

in a mammal and in the labyrinth that corresponds to the proximal tubule the concentration of chloride remains the same as in the blood but in the nephridial canal the concentration of chloride decreases and the urine becomes hypotonic

In all other invertebrates and vertebrates the mechanism for formation of a hypotonic urine appears to be the same Either fluid from the coelomic cavity or a filtrate from the blood moves through the proximal and distal tubules In the proximal tubule it remains isotonic to the blood but in the distal tubule it becomes hypotonic through reabsorption of salt In many marine animals the ability to dilute the urine is missing and in these animals it is found that the distal tubule is missing This is true in fish as well as in crustaceans or annelids

In the kidney of bird and mammal both proximal and distal tubules are present and these animals can also make a dilute urine Even the kangaroo rat which never drinks water in its wild habitat and normally produces a tremendously concentrated urine (about 6 or 7 Osm) makes a *highly* dilute urine when given diluted milk as the only source of food

Micropunctures on rat and guinea pig kidneys were first performed by Walker and associates[3] from the cortical surface where the proximal and distal convoluted tubules of short looped nephrons are accessible (Fig 1 *C*) Through these studies and through other studies by Wirz[4] and by Gottschalk and Mylle[5] it was shown that whereas the fluid along the proximal convolutions remains isosmotic to the blood the fluid in the early distal convolutions is distinctly hyposmotic

Wirz showed that when the rat is in water diuresis the fluid in the distal convolutions remains hyposmotic When the animal is producing a concentrated urine the fluid is still highly hyposmotic in the early distal convolutions but becomes isosmotic to the blood as it proceeds toward the distal end of the distal convolutions These later findings were beautifully confirmed by Gottschalk and Mylle The results are similar to the findings in the earthworm and the crayfish in that the osmotic concentration remains identical to that of the blood in the proximal tubule but becomes lower in the distal tubule Thus also in mammals the function of the distal tubule is distinct from that of the proximal tubule in that the tonicity of the fluid inside the tubule is lowered through the active reabsorption of salt by the tubular wall In the proximal tubule too there is active reabsorption of Na^+ but in the proximal tubule the permeability to water is so great that no difference in tonicity can be detected with available methods

The ultrastructures of the tubular cells that are capable of creating a difference in tonicity are remarkably alike Electron micrographs of a cell from the distal tubule of a mouse[6] and from the nephridial canal of a crayfish[7] show deep basal infoldings with mitochondria lined up between the infoldings These cells also resemble those of the ducts of salivary glands and sweat glands for which the same function namely the active reabsorption of salt has been shown

The next question must be Since the renal tubules are functionally alike why can the crayfish and the earthworm make a hypotonic or isotonic urine only whereas a mammal can make a urine that is several times as concentrated as the blood?

The answer is found in another part of the renal structure the loop of Henle The only animals that possess the loop are the birds and the mammal In the lower vertebrates (fish amphibians reptiles) the renal tubules are convoluted throughout their length In the birds most of the nephrons are of the reptilian type but in addition there are some with a loop of Henle In the mammals all the nephrons have a loop some short and some long It is an important feature that the loops are parallel with each other and parallel with the collecting ducts and with the capillaries (see Fig 1 *C*)

The function of Henle s loop has been very poorly understood until quite recently It was suggested by Peter (1909) that the length of the thin segment is related to the maximal concentration ability and that active reabsorption of water takes place in the thin segment This notion however was discarded partly on a histologic basis The cells in the walls of the limbs simply did not look as though they were able to do osmotic work H W Smith (1950)

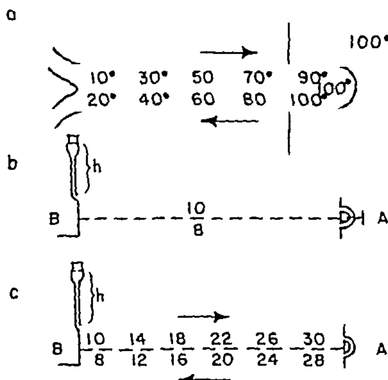


Fig. 2. ... countercurrent ... A pipe ... the water ent... with the temperature of 100°C. ... the hairpin-... heated ... the ... modified from Hargitay and Kuhn. The ... is filled with ... solution. The ... is closed. Due to the difference in hydrostatic pressure between the upper and lower part of the tube the water diffuses across the semipermeable membrane and the solution in the lower part becomes dilute compared to that of the upper part. ... countercurrent multiplier system ... this system the force which creates the osmotic gradient ... the hydrostatic pressure difference between the two tubes. (In the kidney the force is not hydrostatic pressure difference but the sodium pump.) If the ... at ... open and steady flow of solution ... the direction indicated by the arrows ... concentration gradient in the tube will be established.

gested that the urine becomes isotonic with the blood in the thin limb. In 1951, however, a paper was published by Hargitay and Kuhn, which has caused something of a revolution in renal physiology—"Das Multiplikationsprinzip als Grundlage der Harnkonzentrierung in der Niere." However, another 5 to 7 years elapsed before these new thoughts became accepted in this country.

The first experimental verifications for this theory were supplied by Wirz, Hargitay and Kuhn[11] and by Wirz.[12] It was shown that the osmotic concentration of the renal tissue rises from cortex through outer and inner zones of the papilla. Samples of blood from the vasa recta at the tip of the papilla were found to have the same osmotic concentration as the simultaneously formed urine. Later, Gottschalk and Mylle[4] showed that also the fluid inside the loop of Henle at the tip of the papilla is isosmotic with the urine.

Hargitay and Kuhn[6] proposed that the loop of Henle functions as a countercurrent multiplier system. Before going into greater detail it is necessary to explain how a countercurrent exchange and a multiplier system operate. Water in a straight pipe is sent through an oven; the temperature of the oven is 100°C. and that of the water in the pipe is 10°C. During the passage through the oven the water attains the same temperature as that of the oven. If 1 liter of water passes through the pipe per minute, then approximately 90 kilo-

calories are removed from the oven per minute. If we designed the system as a countercurrent exchange system, however, we could send the same amount of water through the oven per unit time but carry only a very small amount of heat out of the oven. This could be done if we bent the pipe so that the incoming stream of water was in close contact with the outgoing stream. Now the outgoing water would give off heat to the incoming stream, and by the time that the water left the system it would be only slightly warmer than that coming in (as shown in Fig. 2 *a*). The heat in the oven would be conserved and a temperature gradient along the loop would be established. This is a typical passive countercurrent exchange system. It could apply equally well to a system in which a *dilute salt solution* was carried through a tube with semipermeable walls into a reservoir containing a more concentrated solution. In this case water would move across from the incoming to the outgoing stream and a concentration gradient along the loop would establish itself. There are several biologic examples of countercurrent exchange systems. In the flippers of seals and whales the arterial and venous blood vessels are in close contact with one another, so that the heat from the arterial blood going to the flipper is given off to the cold venous blood which is returning. In this way the blood is cooled before it reaches the flipper and loss of heat to the surrounding water is minimized.

In the swim bladder of fish a very beautiful example of a countercurrent exchange system is found in the rete mirabile, the blood supply to the gas gland. (The rete mirabile probably also functions as a countercurrent multiplier system, but this aspect of its function will be disregarded here.) In the rete the incoming arterioles split up into numerous capillaries, which are completely interspersed between the outgoing venous capillaries. The arrangement is so perfect that each arterial capillary is surrounded on all sides by venous capillaries and vice versa.[13] The functional significance of this arrangement is that oxygen can diffuse readily from venous to arterial capillaries, and thus the high oxygen pressure in the swim bladder is preserved.

In the mammalian kidney the vasa recta are arranged in capillary bundles. A recent study[14] of these bundles has revealed that the structure resembles very closely the rete mirabile of the swim bladder with the same complete interspersion between venous and arterial capillaries. From what is known at the moment, the capillaries function as a passive countercurrent exchange system in the kidney. In other words, they can maintain a difference in concentration but they cannot create it.

A countercurrent system in which a difference in concentration is created is a *multiplier system*. In such a system a force is needed and energy must be expended. Hargitay and Kuhn in their original model proposed that the force that caused concentration of the glomerular filtrate in the *loop of Henle was the hydrostatic pressure*. This has since been shown not to be the case, but I will use their model to show how a multiplier system can operate. The system is shown in Fig. 2. Both the upper and lower tubes are filled with the *same* salt solution. The membrane which separates the two solutions is permeable to water but *not* to salt. First, we close the valve at *A*. The higher hydrostatic pressure in the upper tube will cause the water to move across the membrane to the lower tube. The solution in the upper tube will become more concentrated and the solution in the lower tube more dilute. A steady state will be reached when the osmotic pressure difference balances the hydrostatic pressure difference (Fig. 2 *b*). Now, if we open the valve, some of the more concentrated solution will flow into the lower tube. Again water will diffuse across. The solution on top will become still more concentrated. The process can be repeated, and each time the concentration near the loop will increase. If a steady slow flow is maintained, the result will be that the concentration at the tip of the loop will be several times higher than the concentration at the inflow and outflow sides (Fig. 2 *c*). This is a true countercurrent multiplier system, and the force is the hydrostatic pressure.

In the kidney the force *is not* the hydrostatic pressure. There is now convincing evidence that the active transport of sodium out of the ascending limb of the

of Henle is primarily responsible for the osmotic concentration gradient created by the loop of Henle When a mammalian kidney is analyzed for a number of solutes it is found that the two substances that contribute to the greatest degree to the osmotic gradient found along the loop of Henle are sodium (with its accompanying anions) and urea The part that sodium contributes is independent of the amount of sodium that appears in the urine

When micro samples are taken out of the proximal and distal convolutions it is found that although the concentration of sodium in the proximal tubule under most circumstances is almost identical to that of the blood it is considerably lower in the early distal convolutions It can be calculated that during the passage through the short loops of Henle about one half of the water that enters and about three fourths to four fifths of the sodium that s leave the tubule [6] Urea on the other hand enters the tubule in the loop of Henle in relatively large amounts i e at th end of the proximal tubule only one third of the filtered urea is left but in the distal convolutions more urea is present than the total amount filtered Where this urea comes from is not quite clear at the moment It may be secreted or it may diffuse into the tubule

The sodium that is actively pumped out of the ascending limb of the loop could either diffuse into the descending limb or remain in the interstitium In the first case it will increase the concentration of salt in the descending limb directly in the second case it will cause water to diffuse out of the descending limb into the more concentrated interstitium In either case the fluid inside the loop of Henle will increase in concentration toward the tip and become dilute again toward the cortex

How is the urine concentrated? During water diuresis when antidiuretic hormone (ADH) is absent from the blood fluid in the distal convolutions remains dilute The distal convoluted tubule and probably also the collecting duct show low permeability to water under these conditions On the other hand when the animal is producing a concentrated urine and ADH is present the distal tubule and collecting duct are more permeable to water Water diffuses out and the total volume of fluid in the tubule is diminished to about one fifteenth to one twentieth of the volume of the filtrate [14] By the time the fluid reaches the collecting duct it is isotonic to the blood Now this small volume of isotonic fluid passes down through the increasingly more concentrated regions of the medulla Water will diffuse out of the collecting ducts into the interstitium and the fluid in the collecting ducts will attain the same osmotic concentration as that in the surrounding tissue and as the fluid in the capillaries and loops of Henle The water that diffuses out of the collecting ducts is carried away by the vasa recta together with some of the salt deposited in the tissue by the ascending limbs of the loops of Henle

The maximum concentration that can be achieved by a countercurrent multiplier system depends primarily on three factors the relative lengths of the multiplier system the concentration difference between the two limbs and the rate of flow through the system The maximum concentration is directly related to the two first factors but inversely related to the square of the rate of flow Since the maximum concentration depends on the length of the multiplier system we should expect to find a correlation between the length of the part of the loop of Henle that acts as *a multiplier system and the ability of* the animal to concentrate the urine If only the outer zone of the medulla were active a thick inner zone should not appreciably increase the concentrating ability If on the other hand the entire medulla acts as a multiplier system one should expect the concentrating ability of the animal to be related to the combined thickness of the outer and inner zones of the medulla

In Fig 3 data on maximal concentrating ability from a number of animals are shown [7] It is seen that there is a rough correlation between the relative thickness of the medulla and the maximal ability to concentrate the urine In the upper graph the maximal ability to concentrate electrolytes and urea are plotted individually against the relative thickness of the medulla The correlation between the thickness of the medulla and the ability to concentrate

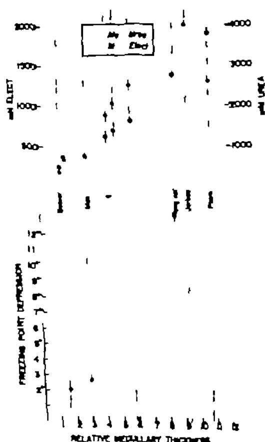


Fig 3 *Lower graph* The maximal urinary concentrations obtained in the different animals are given as freezing point depressions and are plotted against the relative medullary thickness of the kidney The figures for the relative medullary thickness are taken from Sperber who defines it as follows The medullary thickness × 10 / kidney size where kidney size = the cube root of the product of the dimensions of the kidney *Upper graph* The maximal urinary concentrations of urea and total electrolytes are plotted against the relative medullary thickness The values for maximal urea and electrolyte concentrations were not obtained in the same samples of urine (From American Journal of Physiology 200 1119 1961)

electrolytes is very good indeed The ability to concentrate urea seems however to vary with other factors It can be seen that three animals the pig the beaver and the Psammomys are not able to concentrate urea as well as electrolytes whereas all the other animals can concentrate urea better than electrolytes The close correlation between the thickness of the medulla and the ability to concentrate electrolytes seems to indicate that not only the outer zone but also the inner zone acts as a countercurrent multiplier system Further indications that this is so can be seen from the fact that in animals like the *Psammomys with a thick inner zone of* the medulla the concentration of sodium continues to increase all the way to the tip of the papilla Furthermore it is found by micropunctures of the thin limb of the loop of Henle that the osmolality is lower higher up on the papilla than closer to the tip [3]

When an animal is making a dilute urine the *osmolality* of the *medulla* is higher than that of the cortex and of the blood but not nearly so high as in the animal making a concentrated urine It would seem that the countercurrent multiplier system is operating also when the kidney is producing a dilute urine but less effectively If the rate of flow i e the flow through the loops of Henle and the *flow through the vasa recta* were *increased* during high diuresis one would expect that the maximal concentration that the countercurrent system could set up would be diminished Therefore it seems quite possible that the rate of flow should be increased during high diuresis This was actually found by Thurau Deetjen and Kramer in studies in which the blood flow in the renal papilla was measured directly by placing photocells on the medulla However Lilienfeld and associates [22] in their studies with I[131] labeled protein came to the opposite conclusion namely *that* during a high flow of urine the flow of blood through the renal papilla is diminished At the moment therefore this question appears to be unsettled

If we return to the earthworm the crayfish and the lower vertebrates we see that what was shown for these animals that the fluid becomes hypotonic in the distal tubule by active reabsorption of sodium is also true of the mammals In other words the mammalian renal tubule does the same thing in this regard as the nephridium in the earthworm (Fig 1) It is only because mammal and bird tubules are bent into loops that they can produce a hypertonic urine whereas all the other tubules (except the Malpighian tubules) can make only hypotonic or isotonic urine The fact this is so is rather remarkable if

it it in another w iy It appears that no animals except the insects c in make the fluid inside the tubule hypertonic by secret ing ions int › it In ill the other kidneys sodium c in be reabsorbed to make the fluid insid the tubules hypotonic and water in move ut passively to make the fluid i side the tubule isotonic with its surroundings Thus it seems that it is impossible for sodium to be actively se creted into the tubules in iny kidney (ex cept in insects) from the most primitive kidney in the innelids to the complicated mamm ili in kidney bc iuse if this were possible we should expect to find some inim ils for ex mple the marine fish or the terrestri il reptiles in which the con centr iti n in urine coul l be it least slightly higher th in th it in the blood

With respect to movements of water these compir tive findings seem to indi ite th it ictive tr insport of water out of ren l tubule is impossible because if this were possible we should expect to find hypertonic urine in some of the inim ls without i countercurrent mul tiplier system

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Annual influenza vaccination as a lifesaving measure

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Since the onset of the 1957 pandemic of Asian influenza there have been repeated recommendations for influenza vaccination with special emphasis on individuals with chronic debilitating disease, pregnant women, and those in the older age groups. The recurrence of influenza A2 in epidemic proportions in the winter of 1959-1960 with the associated increased mortality showed how infrequently these recommendations had been followed. Apparently most individuals had not yet grasped the enormousness of the disease nor understood that they might die as a result of influenza. In order to increase the number of vaccinees, medical personnel who care for aged or chronically ill persons should offer considerably more encouragement for and should provide an organized approach to annual immunization. Hospital and clinic staffs as well as practicing physicians must consider influenza vaccination as an essential phase of management of their high-risk patients. In addition to preventing about three fourths of the excess cardiovascular-renal and pneumonia complications and deaths due to influenza, hospital operating costs would be reduced, since therapy of a single case of staphylococcal pneumonia could equal the expense of an entire vaccination program.

The general public as well as most physicians are aware that the large influenza pandemics of 1918-1919 and 1957-1958 caused the death of millions of persons throughout the world. It has not been so well appreciated that excess mortality directly associated with outbreaks or epidemics of Type A or B influenza virus can be shown in many of the intervening years. This type of information is compiled continuously by the Epidemiology Branch of the Communicable Disease Center, United States Public Health Service. Also studies which include the periods 1887-1956 and 1957-1960 have clearly shown the excess mortality due to this disease. It was estimated that 86,000 excess deaths occurred during the period from 1957 to 1960 in the United States alone. Of special interest to readers of this Journal was the observation that more than half of these excess deaths occurred in persons with cardiovascular-renal disease and over two thirds of the total were in those who were 65 years of age and older. This represents a transition since the 1918-1919 epidemic when 92 per cent of the excess was due to influenza and pneumonia. During the past 10 to 15 years only a fourth of the deaths have been due to this cause.

Clinical studies have documented the association of rheumatic heart disease and influenza-associated deaths. The occurrence of influenza virus pneumonia in patients with mitral stenosis has been frequently noted and it has been suggested that pulmonary hemodynamic factors may be of significance in pathogenesis. The dangers of influenza to pregnant women

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Rec[illegible] publica[illegible] [illegible]

have also been the subject of clinical observations that have described increased numbers of cases of fatal pneumonia during epidemics. This is not too surprising since most infectious diseases are more severe during pregnancy. Other conditions that place a patient in the high risk group include chronic pulmonary disease and metabolic disorders such as diabetes mellitus.

The following recommendations for vaccination against influenza in the civilian population have been made by the Surgeon General's Advisory Committee on Influenza, July 31, 1961:

Experience with Asian influenza between 1957-1960 has served to re-emphasize that patients in certain disease categories who acquire influenza are at much greater risk of death or severe morbidity than the normal population or patients with miscellaneous diseases. In order to reduce the ... to patients at high risk, it is recommended that they be immunized with polyvalent influenza vaccine as soon as practicable after September 1 and no later than the beginning of the usual influenza season in late December. Since a 2 week delay in the development of antibodies may be expected, it is important that immunization be carried out before epidemics occur in the area.

The adult dosage recommended by the Advisory Committee for primary immunization is 1.0 c.c. (500 CCA units) of polyvalent vaccine administered subcutaneously. It is urged that persons who have not previously been immunized should also receive, if feasible, a second dose of 1.0 c.c. approximately 2 months after the first injection. This second dose will serve to protect the small but significant proportion who do not develop adequate antibody after the first injection. Persons previously immunized should be reinoculated with a single booster dose of 1.0 c.c. subcutaneously each year.

Patients in the following disease categories have experienced the highest mortality rates, and therefore specific protection is clearly indicated for them as a routine practice:

A. Persons at all ages who suffer from chronic debilitating disease, e.g., chronic cardiovascular, pulmonary, renal, or metabolic disorders, in particular: (1) patients with rheumatic heart disease, especially those with mitral stenosis; (2) patients with other cardiovascular disorders such as arteriosclerotic heart disease and hypertension, especially those with evidence of frank or incipient cardiac insufficiency; (3) patients with chronic bronchopulmonary disease, for example, chronic asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, pulmonary tuberculosis; (4) patients with diabetes mellitus; (5) patients with Addison's disease.

B. Pregnant women.

C. All persons over 65 years of age.

In years of expected high incidence, vaccination *is recommended* for the following groups of people: (1) persons in medical and health services, public safety, public utilities, transportation, education, and communications; (2) persons in age groups in which influenza occurs in highest incidence, namely, 5 to 25 years.

Dose and schedule of vaccination by age

1. *Adults (i.e., individuals 13 years of age or older)*. A dose of 1.0 c.c. (500 CCA units) should be administered subcutaneously as soon as practicable after September 1 and no later than January 1. Those not previously immunized should receive, if feasible, a second dose of 1.0 c.c. approximately 2 months after the first injection.

2. *Children aged 6 to 12 years*. A dose of 0.5 c.c. (250 CCA units) should be administered subcutaneously as soon as practicable after September 1 and no later than January 1. Those not previously immunized should receive, if feasible, a second dose of 0.5 c.c. approximately 2 months after the first injection.

3. *Children 3 months old to preschool age*. Initial doses of 0.1 to 0.2 ml. (50 to 100 CCA units) should be administered subcutaneously on two occasions separated by interval of 1 or 2 weeks. A booster inoculation of the same strength should be given, if feasible, 2 to 3 months later. Preferably, the schedule of vaccination should be completed by January 1. Since febrile reactions to vaccine in this age group may reach an incidence of 20 per cent, it is suggested, when not contra-

indicated that acetylsalicylic acid (one gram per year of age) be given every 6 hours for the first 24 hours

4 *Persons previously immunized with polyvalent vaccine* Each fall prior to January 1 persons previously immunized with polyvalent influenza virus vaccine should be reinoculated with a single dose according to the following schedule children 3 months old to preschool age—0 1 to 0 2 ml children aged 6 to 12 years—0 5 ml adults—1 ml

Except to warn against the serious consequences of influenza in the high risk group it should not be necessary to recommend repeatedly a vaccine that has been of value in military and industrial populations for many years[11] In addition to preventing morbidity from the illness or complications and occasional deaths in these groups and even in children the question of permanent damage to the cardiovascular system and cellular metaplasia in the tracheobronchial epithelium needs much more consideration[13 14] Physiologic abnormalities can be readily demonstrated during the acute phase of influenza by electrocardiography spatial vector cardiography and digital rheoplethysmography[14] Information on the degree of permanent residual changes if any in the heart and blood vessels and the bronchial epithelium is certainly needed for influenza as well as other common respiratory illnesses Perhaps a considerable lengthening of the lifespan could be achieved by eliminating these illnesses

Even though there is sufficient justification for administration of influenza vaccine to all individuals on an annual basis the cost inconvenience and voluntary behavior of most of the population makes this degree of refinement in the practice of preventive medicine unlikely for the immediate present The threat of an impending epidemic can serve to stimulate interest in vaccination but accurate predictions cannot be made often enough Other incentives in the form of additional viruses such as adenoviruses or parainfluenza 1 sometimes make immunization more desirable by providing a hope although not based on data for elimination of all respiratory illnesses during the approaching season An adequate all purpose respiratory disease vaccine which contains all the major viruses undoubtedly would solve many of these problems by virtue of its selling features but progress has been slow on such a preparation Perhaps the use of adjuvant preparations will allow more viruses to be combined in a single injection with longer lasting antibody titers Until these vaccines of the future are demanded by an enlightened population it behooves all of us to do what is necessary to apply an efficacious vaccine to the prevention of the most serious of the respiratory illnesses influenza

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Clinical communications

Congenital pulmonary atresia with intact ventricular septum Clinicopathologic correlation of two anatomic types

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Warren E Greenwold M D
James W DuShane M D
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Congenital atresia of the pulmonary valve with intact ventricular septum although a fairly infrequent malformation is by no means rare Peacock in 18[illegible]1 stated that he had knowledge of 8 or 9 such cases Abbott included the description of 10 cases in her atlas Keith and associates[3] mentioned 24 patients with this malformation who were seen at the Hospital for Sick Children in Toronto

Most of the case reports have emphasized the presence of a diminutive right ventricle with thick muscular wall or an absence of the right ventricle In 19[illegible]0 Glaboff and co workers reported a case which was characterized by a dilated right ventricular chamber and mentioned that to their knowledge only one other similar anomaly had been reported in the literature namely a case cited in Abbott s atlas

In 1956 Greenwold and associates presented evidence which correlated each anatomic type with its specific electrocardiographic and radiologic pattern they also emphasized the importance of accurate diagnosis of those cases in which a normal or large right ventricular chamber was present because of the potential for surgical correction or palliation in such instances

It is the purpose of this paper to report the essential clinical and pathologic features in 20 cases observed at necropsy to distinguish further the electrocardiographic and roentgenologic features of one group when contrasted with those of the other and to emphasize the possibility of direct surgical treatment when a right ventricle of normal or larger size is present

Material

The heart collection of the Mayo Clinic (approximately 800 specimens) contains 20 hearts with atresia of the pulmonary valve and an intact ventricular septum This anatomic material was reviewed together with the clinical histories roentgenograms electrocardiograms and laboratory data These hearts include the one described by Williams and associates 1951 and

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Fig. 1. Congenital pulmonary atresia with intact ventricular septum ... small right ventricular cavity (Type 1). Pulmonary artery (P) and aorta (A) in Case I. The fused commissures of the atretic pulmonary valve are clearly seen. The diameter of the pulmonary artery is about half that of the aorta. b, Case VI showing the tiny right ventricular cavity and thick ventricular walls, the small but normally formed tricuspid ... and the fairly large right atrium. (Reproduced with the kind permission of the publisher, Charles C Thomas, from *Atlas of Congenital Anomalies of the Heart and Great Vessels*, ed. 2, 1954, by J. E. Edwards and associates.) c, Case I showing the small right ventricular chamber.

those mentioned by Greenwold and co-workers. Ten specimens, most of them accompanied by clinical, radiologic, and electrocardiographic data, have been sent for examination to one of us (Edwards) by physicians outside the Clinic.

Anatomic features

Nineteen of the hearts were available for current review; another one had been returned to the sender, but the description and photographs of the specimen made at the time of the initial examination were available for study.

The most striking finding, as already mentioned, was the obvious division of the specimens into two categories, namely, those with a small or tiny right ventricular cavity (hereinafter designated as Type 1) and those with a normal-sized or large right ventricular cavity (Type 2). Thirteen hearts were Type 1 and 7 were Type 2. For reasons to be discussed, one heart with a normal-sized ventricle was considered to be Type 1.

By the term *atresia* we mean the absence of any opening whatsoever. In all of the cases which form the basis of this report, atresia was present at the level of the pulmonary valve. They are to be distinguished from those cases in which the pulmonary valvular obstruction is associated with some opening, however small. The latter situation is designated as ***pulmonary stenosis***.

Pulmonary valve and pulmonary trunk. In all cases of pulmonary atresia with intact ventricular septum reported herein, the obstruction was at the level of the valve. The pulmonary valve was represented by an imperforate fibrous membra-

For acknowledgment, see page 60

measured approximately 2 to 3 mm in diameter and which was at times dome shaped (Fig 1 a) Along the pulmonary face of the membrane three equidistant raphes radiated from the center to the periphery of the membrane The valve in these cases bore a striking resemblance to that in congenital pulmonary valvular stenosis except of course for the absence of an opening at this level

The pulmonary trunk was narrower than the aorta in all cases it varied from a diameter which approached that of the aorta to one which was half the size of the aorta At its origin it had a peculiar funnel shaped appearance—extremely narrow at the valve and widened peripherally

Right ventricle In cases of Type 1 heart the right ventricular chamber could be described with one exception as either small or tiny and it stood out in great contrast to the usual tremendous hypertrophy of the wall of this chamber (Fig 1 b and c) In one case an organized thrombus filled the entire right ventricular cavity and another thrombus obliterated the pulmonary trunk

Nine hearts showed anomalous coronary vessels coursing between the right ventricular chamber and the coronary arteries A small dimple was present on the surface of the epicardium where these anomalous vessels entered the epicardium Within the muscle the anomalous vessels arose from sinusoids which were present in the right ventricular wall and communicated with the right ventricular cavity (Fig 2) These vessels are said to be embryologic channels which persist because the extreme right ventricular pressure forces blood through them [15] One heart with a right ventricular cavity of normal size was classified as Type 1 because of the presence of an anomalous coronary vessel

In Type 2 hearts the less common form the right ventricular chamber was usually of normal size (Fig 3 a and b) The wall was thicker than normal but the dispro portion between the size of the wall and the cavity which was characteristic of Type 1 was not evident The right ventricle in Type 2 hearts had a general appearance similar to that of hearts in which there was pulmonary stenosis with intact ventricular septum None of showed the muscular infundibular stenosis that may be present in some instances of pulmonary valvular stenosis In 3 cases the right ventricular cavity was larger than normal (Fig 3 c)

Tricuspid valve A striking and perhaps basic difference was shown by the tricuspid valve in the two types The tricuspid valve in the Type 1 heart was tiny and in keeping with the size of the right ventricular chamber (Fig 1 b and c) Despite its small size the valve had the usual valvular and chordal components and it appeared to be competent In one case in which fluid



Fig 2 Anomalous communication of right ventricle with branches of coronary arteries in 2 patients with small right ventricular chambers and apparently competent tricuspid valves Specimen from 3 month-old infant, showing cross section through right ventricular wall and large intramyocardial sinusoid The latter extends from the right ventricular cavity (R V) to the epicardium (E) where it communicates with branches of the coronary arteries b From 43-day-old infant A large sinusoid (S) that communicates ventricular cavity lea es the right card um and t the per joins ing coronary artery (C A)



Fig 3 Congenital pulmonary atresia with intact ventricular septum and normal sized right ventricular cavity (Type 2) a Case IX showing markedly small right ventricle and malformed tricuspid valve with thickened and shortened leaflets and chordae tendineae b Case X showing normal-sized right ventricle and large right atrium with low insertion of septal leaflet of tricuspid valve (Reproduced with the kind permission of the publisher Charles C Thomas from Edwards J E in Gould Pathology of the Heart ed 2 1960) c Case VII with large right ventricle and the malformed tricuspid valve with partial [illegible] of the posterior and septal leaflet to the ventricular septal wall (see Fig 3 d)

was injected into the right ventricular chamber the tricuspid valve was shown to be competent

In Type 2 hearts the circumference of the tricuspid orifice corresponded to the size of the right ventricular chamber In every case but one the anatomic evidence suggested valvular incompetence The malformations which affected the tricuspid valve in these 6 hearts were of two main types Three hearts had nonspecific shortening of the chordae tendineae and leaflets of the tricuspid valve (Fig 3 a) In one of these 3 cases the edges of the leaflets were rolled and thickened in another the chordae to the anterior leaflet were fused in a conglomeration of fibrous tissue before joining the papillary muscle In 3 hearts the tricuspid valve showed disturbances in development which bore some resemblance to those seen in Ebstein's malformation (Fig 3 b-d) In one of these specimens for instance the posterior leaflet took origin not from the annulus fibrosus but from the right ventricular wall above this anomalous attachment and still below the tricuspid annulus some fibrous valve like tissue was attached both proximally

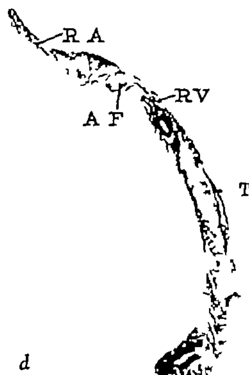


Fig 3d Case VII showing attachment of the abnormal posterior tricuspid leaflet to the right ventricular wall R A Right atrial wall A F Tricuspid annulus fibrosus R V Right ventricular wall T Posterior leaflet of tricuspid valve making several attachments to the right ventricular wall each considerable distance inferior to the annulus fibrosus (Elastic tissue stain X4)

and distally to the right ventricular wall. The septal leaflet of the tricuspid valve in this case was composed of translucent soft tissue that did not completely fill the space between facing ends of the anterior and posterior leaflets. The other two hearts had similar malformations except for minor variation.

Right atrium. In all cases the venae cavae and coronary sinus were properly placed and the right atrial wall was somewhat thicker than normal. An important difference existed in the two types in that the right atrial chamber of the Type 1 heart was somewhat enlarged, whereas the enlargement in the Type 2 heart was generally of striking proportion (Fig. 3, *b*).

Atrial septum. An interatrial communication was present in all cases—a foramen ovale with a competent valve in 16 instances and an atrial septal defect in 4.

Left side of heart and aorta. The left side of the heart was normal save for somewhat larger dimensions of the chambers and valves. All hearts suggested an increased thickening of the left ventricular wall. The aortic valve was normal, and the coronary arteries arose normally. The ascending aorta and the pulmonary trunk were interrelated in the usual fashion. The aorta appeared to be a little larger than normal. In each case the aortic arch was on the left side.

Ductus arteriosus. In each specimen which included the ductus arteriosus this vessel was patent. Often, however, the ductus had a cordlike feel and appeared to be undergoing normal postnatal anatomic obliteration of its lumen. Two specimens showed a thrombosis of the pulmonary end of the ductus, which caused partial occlusion in one and complete occlusion in the other.

Pulmonary vasculature. The pulmonary arterial tree in instances of pulmonary atresia is of interest because the muscular pulmonary arteries in most cases show pronounced thinning of the media when compared with pulmonary vessels of normal infants of the same age group. This is especially true when the ductus arteriosus is relatively long and narrow. Calculation of the ratio between medial tissue and pulmonary parenchyma suggests that this diminished thickness is caused by atrophy rather than by dilatation of the arteries.[11]

Clinical features

Sex. The sex was recorded in 17 cases: there were 6 females and 11 males.

Clinical history. A clinical history was available in 16 cases. Cyanosis was the most remarkable and constant clinical feature; it was noted during the first 24 hours of life in 15 patients and at [illegible] hours in 1 patient. Except for 2 patients in whom it was severe, cyanosis was usually of a mild degree at rest, increased greatly with feeding or crying, and improved, sometimes to the point of disappearing, with the administration of oxygen. Dyspnea was a feature in most patients at one time or another.

Physical examination. Two patients had a systolic thrill at the left lower [illegible] border; these 2 patients had a Type [illegible] heart and both had a severely [illegible] tricuspid valve. All but 3 patients had systolic murmur of variable [illegible] which was heard mostly at the left [illegible] sternal border. In 3 patients the murmur had disappeared shortly [illegible]. One patient also had a continuous [illegible] of moderate intensity at the left [illegible] [illegible] border. The second sound [illegible] tioned was described as [illegible] clicking in most instances [illegible] in one patient and [illegible] another.

The liver was of norm[illegible] of the initial examina[illegible] child with a Type 1 [illegible] age of 8 days and [illegible] liver was palpable 2 [illegible] the costal margin [illegible] liver enlarged shortly [illegible]. The lungs were [illegible] all but 2 patients [illegible] rales were noted [illegible] but disappeared [illegible] patient rales we[illegible] day of life [illegible].

Except for the [illegible] mentioned thrill [illegible] border in 2 [illegible] possibly caused [illegible] there was no [illegible] which character[illegible] [illegible] ld be d[illegible] [illegible]

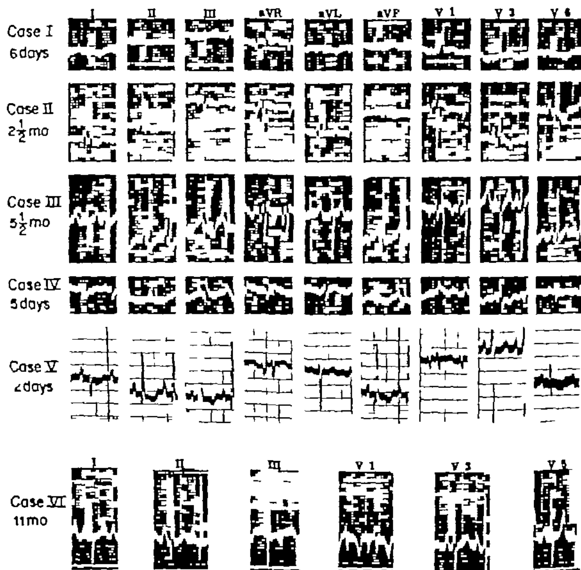


Fig. 4. Electrocardiograms in cases of Type 1. Tracings from patients who were more than 1 week of age show left ventricular dominance, evidence of atrial enlargement, and small or absent R wave in Lead aVR.

Oximetry. Ear oximetry was done in 3 patients (Table I). The oxygen saturation at rest ranged from 60 to 65 per cent and decreased considerably after exercise in one patient. The saturation increased slightly in 2 patients who breathed oxygen during oximetry.

Mode of death. The age at death was known in 18 cases; it ranged between 2 days and 11 months. Sixteen patients died when they were less than 6 months old, 13 when they were less than 3 months old, and 4 during the first week of life. No significant difference was noted between the two groups (Types 1 and 2) in so far as the age at death was concerned.

In the great majority of cases death came rapidly and unexpectedly, most often during an episode of increased cyanosis and dyspnea. A few infants showed the classic picture of congestive heart failure with a liver which enlarged shortly before death. Two patients (one with a Type 1 heart and one with a Type 2 heart) died shortly after a Brock valvulotomy. In another case, a procedure to produce a shunt was planned, but the patient died at the beginning of the operation. Acute pyelonephritis was the precipitating factor in the death of another patient.

Associated malformations or defects, including esophageal atresia, imperforate

aria and Mongolism were found in 3 patients none of these conditions was the precipitating cause of death

Electrocardiographic aspects

The electrocardiogram was available for review in 10 cases including 6 cases of Type 1 and 4 of Type 2. The tracings were evaluated according to our experience with various types of congenital heart disease relative to right and left ventricular overload[14] atrial enlargement and the direction of the ventricular depolarization vector in the frontal plane[18]

In patients who were more than 1 week of age a significant correlation with the anatomic findings was found which apparently reflected the hemodynamic situation before death

Four patients of Type 1 who were more than 1 week of age showed atrial enlargement and left ventricular dominance for age (Cases II III V and VI in Fig 4). In 2 of these patients the mean manifest electrical axis of the QRS complex was +110 degrees in the other 2 it was +15 and +90 degrees respectively. In 2 other patients with a Type 1 heart both of whom were less than 1 week of age the electrocardiogram was atypical showing an axis of −10 degrees at 24 hours and −30 degrees at 6 days atrial enlargement and right ventricular overload in one (Fig 4 Case I) and an axis of +110 degrees some atrial enlargement and normal ventricular complexes in the other (Fig 4 Case IV)

Three patients with a Type 2 heart who had electrocardiograms taken at 13 days and 6 weeks in one and at 14 days and 7 weeks respectively in the other two showed an axis between +105 and +145 degrees atrial enlargement and right ventricular overload. All three had q waves in Lead V. One also showed evidence of good left ventricular potential (Fig 5 Case IX). Another patient with a Type 2 heart who died at the age of 2 days had an atypical tracing which showed some atrial

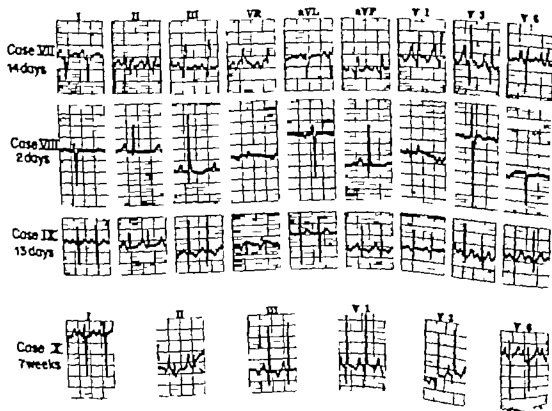


Fig 5 Electrocardiogram in cases of Type 2. Note the presence of qR pattern in Lead V and tall peaked waves in Cases VII IX and X. The changes are interpreted as resulting from right ventricular hypertrophy

Table I Arterial oxygen saturation (per cent) measured by ear oximetry in congenital pulmonary atresia with intact ventricular septum three cases

Case	Type	Breathing air: Rest	Breathing air: Exercise	Breathing oxygen: Rest	Breathing oxygen: Exercise
VII	2	65	Stable	—	—
VIII	2	60	7	70	—
VI	1	64	38	74	28

enlargement and an axis of +120 degrees (Fig 5 Case VIII) All of these patients had malformed tricuspid valves

All except one patient had a clockwise QRS vector loop in the frontal plane with the main area of the loop below the horizontal In Case I the loop was counterclockwise with its main mass in the quadrant extending from 0 to −90 degrees

Roentgenographic aspects

Posteroanterior roentgenograms of the thorax were available for review in 11 cases which included 8 of Type 1 and 3 of Type 2 (Fig 6) The pulmonary vascularity was decreased in all instances In most cases the difference between the two anatomic types was obvious In general Type 1 patients had hearts of normal or moderately increased size with a normal right border (Fig 6 a i) Infants who died when they were less than 1 week of age tended to have larger hearts (Fig 6 d e and h) In most patients the region of the main pulmonary artery was concave with the apex downward and to the left

Type 2 patients had grossly enlarged hearts with prominence of the right border (Fig 6 j l)

When serial roentgenograms were made both types showed progressive enlargement of the heart although the Type 1 hearts never reached the gigantic proportions of certain of the Type 2 hearts

Special mention should be made here of Case V (Type 1 Fig 6 c) in which the thoracic roentgenogram showed evidence of severe cardiac enlargement with a contour indistinguishable from that seen in Type 2 hearts This patient a 13 day-old boy was in cardiac failure when this roentgenogram was taken Necropsy showed this heart to have the largest right atrium of the group and an extremely small patent foramen ovale

Angiocardiography

One patient (Case V) underwent selective angiocardiography The opaque medium was injected successively into the right ventricle and the left atrium The left atrial injection was not remarkable except that it demonstrated simultaneous filling of the aorta and pulmonary artery through a patent ductus arteriosus The right ventricular injection demonstrated dilated myocardial sinusoids and anomalous coronary vessels in the wall of the right ventricle (Fig 7)

Cardiac Catheterization

The same patient (Case V) also underwent catheterization of the right side of the heart the results are summarized in Table II The left atrium was entered through an interatrial opening Three curves were obtained after the injection of 5 mg of Cardio Green Indicator dilution curves were recorded at the femoral artery after injection of Cardio Green into the inferior vena cava the right atrium and the right ventricle All three curves were similar in shape they showed appearance times of 3 to 5 seconds and large initial deflections with extremely slow clearance of dye from the circulation These curves were thought to indicate the presence of an extremely large right to left shunt the close similarity between the curves from the right side of the heart

Table II Data on cardiac catheterization in Case I

Site	Pressure (mm Hg)	O_2 saturation (%) by cuvette oximeter
Superior vena cava	13/3	31
Inferior vena cava	11/3	24 to 43
Right atrium	—	35
Right ventricle	137/10	42
Left atrium	17/11	73
Femoral artery	85/42	74

Cardiac catheterization was performed by Dr H J C Swan

and those from the left atrium suggested that a common route of egress to the systemic circuit existed

Comment

In patients with pulmonary atresia and intact ventricular septum who present a

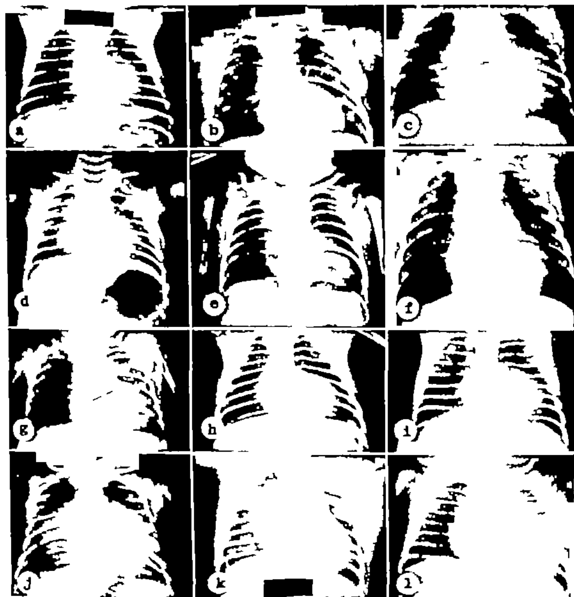


Fig 6 Thoracic roentgenograms in patients th pulmonary re ia and t ict entr cular septum Type 1 j l Type 2 Unle otherwise specified the roentgenogram ere ade fe da bef re death and b Case VII taken t 1 month and 5 months of age re pecti el Note the p ogre n but moderate cardiac enlargement Case V taken t 13 day of ge Thi patient had an extremel mall interatrial communication and the largest right trium of thi group d Case IV taken t 3 day of age This patient had a right entricle of normal ze but the heart as cla fied as Type 1 because of the presence of anomalous coronary essels emanating from the right entricle and normally formed tricu pid val Note the promi ence of the right trial shadow Case II taken at 3 da of age f Case III taken t 5 mo ths of age g Case VI taken t 11 month of age (Reproduced with the kind permi ion of he publ her Charles C Thoma from *A Atlas of Congenital Anomalies of the Hea t nd Great Vessel* ed 2 1954 by J F Ed ard and sociates) h Film from 3 day old patient Case I taken t 5 day of age j Case X taken t 48 da of age The patient died 10 day later (Reproduced w th the kind permission of the p bl her Charles C Thoma from Edward J E in Gould *Pathology of the Heart* ed 2 1960) k Case IX taken t 11 da f age The patient died 40 da later shortly after Brock procedure l C se VIII taken 1 d of



F 7 Case V Frontal and lateral angiocardiograms in a 18-day-old patient who had pulmonary atresia with intact ventricular septum and small right ventricle Myocardial sinusoids (M.S.) and an anomalous coronary vessel (C.S.V.) are clearly seen Necropsy revealed that this vessel emptied into the anterior descending coronary artery This patient died after an unsuccessful Brock procedure

small right ventricle the tricuspid valve though small appears to be normal in shape and apparently is competent The right ventricle (Fig. 8) which has no path of egress hypertrophies concentrically and forces blood through the only possible escape namely the embryologic myocardial sinusoids and thus keeps them wide open after birth Because of its small cavity and thick walls which offer great resistance to filling the right ventricle in itself would constitute an obstacle to proper flow should the valvular obstruction be relieved Opening of the pulmonary valve might not correct the patient's hemodynamics sufficiently to assure survival in the immediate postoperative period Also the virtual absence of a right ventricular outflow tract in these cases makes it extremely difficult and hazardous to perform a Brock operation A procedure to produce a shunt probably would be better in these cases

On the contrary 6 of the patients who had right ventricles which were normal in size or enlarged had tricuspid valves that presented gross anatomic malformations which more than likely were severe enough to cause valvular insufficiency This tricuspid incompetence appears to be responsible for the development of the right ventricle by allowing a ready path of egress for the blood during ventricular systole The stimulus for anomalous coronary connections does not exist and we were unable to demonstrate them in any of these patients This lesion is we believe potentially amenable to operation without the use of extracorporeal circulation as demonstrated in the following case

Case IX A week-old white boy was admitted to the hospital in June 1953 with history of cyanosis and a heart murmur since birth During the week preceding admission he had had frequent spells of anoxia especially at the time of bowel movement Examination revealed severely cyanotic child with clubbing of the fingers and toes and harsh systolic murmur with thrill at the third and fourth left intercostal spaces The lungs were clear The liver was felt two fingerbreadths below the right costal margin The electrocardiogram showed atrial enlargement and right ventricular overload (Fig 5) The thoracic roentgenogram showed clear lung fields and pronounced cardiac enlargement (Fig 6) A diagnosis of pulmonic stenosis was made.

Through a transventricular approach a probe was passed forcibly from the right ventricle into the pulmonary artery followed by a Potts dilator open to 6 mm The patient presented an immediate and striking improvement in color and did fairly well for 2 or 3 hours after operation However Cheyne-Stokes respiration soon developed along with an irregular heart rate and the infant died 5 hours after operation Necropsy disclosed that the valvotomy had been made at the periphery of the valve and had resulted in only a partially effective opening

The importance of differentiating clinically between Type 1 and Type 2 hearts

is evident. We believe that this can be done fairly easily in patients who are more than 1 week of age. In a cyanotic child in whom the lungs are clear, the presence of a normal-sized or moderately enlarged heart and an electrocardiogram which shows right axis deviation with left ventricular dominance would point toward the diagnosis of pulmonary atresia with intact ventricular septum and a small right ventricle; the right axis deviation differentiates it from tricuspid atresia. Conversely, a similar patient who presented evidence of pronounced enlargement of the heart with right ventricular overload on the electrocardiogram most likely would have a right ventricle of normal size or larger (Type 2).

In patients who are 1 week of age or younger the clinical diagnosis was, in our experience, almost impossible because the electrocardiogram and thoracic roentgenogram were atypical. In one patient the QRS axis was −60 degrees, which fact made the differentiation of this anomaly *from tricuspid atresia extremely difficult.*

Angiocardiography and cardiac catheterization should be used when the diagnosis is in doubt, but these procedures are not necessary in every case since the risk from the tests alone is fairly high and the results are not always diagnostic.

Of all the diagnostic procedures available, selective angiocardiography which delineates the right ventricle, when possible to perform, is probably the most valuable. It should help to obtain better information as to the size of the right ventricular cavity, and the demonstration of the abnormal myocardial sinusoids should point to the diagnosis of pulmonary atresia of Type 1. To our knowledge, this is the first time that these anomalous vessels have been demonstrated by angiocardiography. Rapid injection of a relatively large quantity of medium into the right ventricle was probably the main factor in obtaining good visualization of the right ventricle and filling of the sinusoids.

Transitional forms of this anomaly may exist. As already mentioned, one patient had a right ventricle of normal size and a fairly normal tricuspid valve and was classified as Type 1 mainly because of the presence of anomalous coronary connections; this patient was less than 1 week of age and the electrocardiogram and thoracic roentgenogram were atypical.

As cases continue to accumulate, the entire spectrum of this anomaly will doubtlessly emerge, the range being from a right ventricle of aneurysmal proportions[3] to one of microscopic size. However, we believe that the pathologic classification into two groups, which has enabled us to properly label 19 of the 20 cases and to correlate the clinical and pathologic findings in most instances, will remain valid.

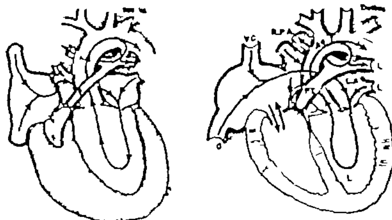


Fig. 8. Diagram of the circulation in patients with a small right ventricle (*left*) and in those with a right ventricle of normal size or larger and tricuspid insufficiency (*right*). (Reproduced with the kind permission of the publisher, Charles C Thomas, from Edwards, J. E., in Gould: *Pathology of the Heart*, ed. 2, 19

Summary

A clinical and pathologic study was made in 20 cases of pulmonary atresia with intact ventricular septum proved at necropsy. The hearts usually could be divided readily into two groups namely those with a small or tiny right ventricle (Type 1) and those with a right ventricle of normal size or larger (Type 2). 13 hearts were of Type 1 and 7 were of Type 2.

In cases of Type 2 the tricuspid valve presented gross anatomic malformations namely nonspecific shortening and thickening of the chordae tendineae and leaflets in 3 instances and malinsertion of the leaflets in 3 others—a defect similar to that encountered in Ebstein's disease. In cases of Type 1 the tricuspid valve was small but well formed. 9 of these hearts had anomalous coronary vessels which connected the right ventricular myocardial sinusoids with the coronary arterial system.

When the patients were more than 1 week of age these two types usually could be differentiated on the basis of radiologic and electrocardiographic findings. This is of considerable importance because of the possibility of direct surgical treatment when the right ventricle is of normal size or larger.

For the 10 heart specimens which were received from outside the Clinic we wish to express our most sincere thanks to the following physicians: Dr T E Lodden Pomona Calif; Dr G D Griffin Roswell N M; Dr R M Knowles Oak Ridge Tenn; Dr J D Barger Phoenix Ariz; Dr Sylvia John San Antonio Tex; Dr F J Fichs ld Great Falls Mont; Dr J B Maxwell Alexandria La; Dr C M Whorten Jacksonville Fla; Dr D L Alcott San Jose Calif

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The flat right atrial border

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In 1957 Soloff and Zatuchni described an angiocardiographic sign of constrictive pericarditis The right lateral border of the opacified right atrium was rigid and had lost its normally outward convexity This feature of constrictive pericarditis was independently described by Figley and Bagshaw [1] and was subsequently also demonstrated in negative-contrast roentgenograms employing carbon dioxide [2] The purpose of this report is to show that such involvement of the right atrium can occur early and is not hemodynamically significant

Case report

G K a 64 year-old white man was admitted to Episcopal Hospital on Jan 19 1961 because of chest pain and shortness of breath A pericardial poudrage had been done by Dr Thomas J E O'Neill on Nov 17 1960 because of intractable pain due to coronary insufficiency since heart attack in 1949 Prior to operation cardiac examination by clinical and roentgenologic method had revealed normal findings An electrocardiogram showed symmetry of the T w es and slight prolongation of the S-T segment which was minimally depressed in leads facing the epicardial surface of the left entricle

Pericardial poudrage was accomplished through small incision in the left fifth intercostal space medially The pericardial ca ity was clean and 5 Gm of talc were inserted Postoperatively the patient course was uneventful other than for the occurrence of left pleuritis Left thoracentesis was performed t ice nd serous fluid was obtained He was discharged on Dec 6 1960

After discharge he continued to ha e an ache in the left hemithorax On the day of readmission a severe episode of pain occurred Pain was aggravated by inspiration and was associated with shortness of breath and a sensation of syncope During hospitalization he was given analgesics nd the symptoms abated There was no fever Examination revealed dullness and decreased breath sound over the left lower hemithorax posteriorly There as no cardiac impulse The heart sound were normal in quality rate and rhythm The jugular eins were slightly distended but filled more rapidly from abov than below nd collapsed with inspiration There was no pul paradoxus The liver and spleen w re not palpable There was no edema

Fluoroscopic examination of the chest re ealed densit in the left lower hemithorax mainly posteriorly con istent with pleural effusion The lef hemidiaphragm w ele ted nd l m ed in motion The cardiac silhouett as normal in ize and shape Border pulsat ons were present throughout Minimal change in size of the cardiac silhouett occurred w th the Val al and Muller maneu ers

Electrocardiographic examination di closed abnormality only of he T w es The T ector was directed minus 122 degrees posteriorly Voltages of the QRS and P complexes w re normal nd un changed compared with preopera iv tracings

Laboratory studies i cluding blood coun nd tra sam se nd tratr ptol ti rs w re normal

Antecub tal enou pressure was 90 mm and circulation times ith ether and Decholin were 8 nd 16 second respecti ely

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Fig. 1. Negative contrast roentgenogram with radiolucency produced by carbon dioxide within the right atrium. Note the flat border. Adjacent density is thicker than in the normal person.

Negative contrast study of the heart was done on Jan. 25, 1961. One hundred milliliters of carbon dioxide were rapidly injected intravenously with the patient in the left lateral decubitus position. The lateral border of the cardiac silhouette in the region of the right atrium was convex outward, and the lateral border of the gas shadow was flat (Fig. 1). The density between these two borders was asymmetrically increased to a maximum of 13 mm. at the summit. These findings were interpreted as being due to constrictive pericarditis and effusion.

Cardiac catheterization was performed on Feb. 16, 1961. The oxygen consumption was 155 c.c./min., arterial oxygen saturation was 92 per cent, and cardiac output was 3.7 L./min. The pressures in millimeters of mercury were: right atrium, 6 (mean); right ventricle, 25/7; pulmonary artery, 25/10; pulmonary wedge, 9-10 (mean); and brachial artery, 150/80. There was no gradient between the superior vena cava and right atrium or between the right atrium and right ventricle. The contour of the right atrial pressure pulse was not M or W in shape. The right ventricular pressure pulse showed no diastolic dip, and the ratio of end-diastolic to systolic pressures was less than 1:3. There was, therefore, no hemodynamic evidence of constrictive pericarditis. The slight reduction in cardiac output and the minimal elevation of end-diastolic pressure in the right ventricle, although not strikingly abnormal, were perhaps due to mild myocardial dysfunction related either to underlying coronary arterial disease or to myocarditis secondary to pericardial poudrage, or to both.

Discussion

In the normal person, contrast roentgenograms reveal a convexity outward of the border of the right atrium outlined by gas or opaque media, and adjacent density is no more than 5 mm. thick. Change in convexity or thickness allows for recognition of pericarditis or effusion or both.[1-4]

A flat right atrial border has been seen to occur only in persons with constrictive pericarditis. At operation, this border of the right atrium was found to be intimately linked with the overlying pericardium.[1] In fact, the linkage was such that the surgeon could not find a plane of cleavage. That this so-called structural abnormality is not necessarily a late phenomenon is indicated by the case reported upon here; in this patient it was found 2 months after pericardial poudrage.

The hemodynamic importance of this finding has not been previously determined, although it was originally suggested to have no functional significance. In fact, Isaacs, Carter, and Haller[6] found that constriction of the right atrium produced experimentally in dogs resulted in no significant hemodynamic abnormality, and Sawyer and associates,[7] in human beings with constrictive pericarditis, observed no fall in pressure between the superior vena cava and right atrium or between the right atrium and right ventricle. Their conclusion that constriction of the right atrium by pericarditis is not hemodynamically significant is supported by our findings.

Summary and conclusions

A case is reported in which negative contrast roentgenography uncovered a flat rather than normally convex outward right atrial border 2 months after pericardial poudrage. Such a finding, although diagnostically meaningful of structural abnormality, does not necessarily signify hemodynamic abnormality.

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Correlation between the shape of the P wave and the length of the P R interval in normal electrocardiograms

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Differences in the shape of the P wave and their correlations with other electrocardiographic elements are indifferently treated in the electrocardiographic literature Correlations between the shape of the P wave and length of the P R interval to the best knowledge of the author have not yet been investigated The present study deals with this particular correlation

The normal P wave in standard leads may present a rounded a peaked or less frequently a notched form The relative frequency of differently shaped P waves is estimated very distinctly by different authorities Shipley and Halloran found rounded P waves in two thirds and peaked P waves in one third of 200 normal electrocardiograms Notching along the course of the P wave occurred in about 30 per cent of the tracings Similarly Stewart and Manning found that in the electrocardiogram of 500 healthy aviators there was an 83 4 per cent incidence of rounded P waves whereas peaked and notched P waves were observed with a frequency of 9 8 and 5 4 per cent respectively In contrast Graybiel and associates[3] found a 41 1 per cent incidence of peaked P waves in the electrocardiograms of 1 000 young aviators and an incidence of 29 4 and 28 2 per cent respectively of rounded and notched P waves These varying shapes of the atrial wave bear different correlations with the length of the P R interval as the present study demonstrates

Methods and materials

Normal records inscribed with a Sanborn Cardiette were used for purposes of the present investigation The P wave the P R interval and the P R segment were examined in Lead II only The duration of the P R segment was calculated by substracting the duration of the P wave from the length of the P R interval P waves were classed according to their shape into three groups (1) peaked (2) rounded and (3) notched A peaked P wave was considered to be present when the acutely pointed apex lasted not more than 0 01 second Only records which exhibited P waves of constant form were used

Normal records which exhibited P R intervals that were from 0 11 to 0 24 second in duration were used in the present investigation It is generally agreed that the commonly observed upper limit of the normal P R interval is 0 20 second However the general consensus is that the P R interval may often last as long as 0 24 second or more in the absence of any other electrocardiographic evidence of a diseased myocardium Thus to extend the present correlative study to the extreme limits of duration of the P R interval records with a P R interval up to 0 24 second were considered to be nor

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Table I Correlation between the shape of the P wave and the length of the P R interval duration of the P wave P R segment and the ratio P/P R segment

	Incidence of P wave			
	Rounded (%) *56.2*	*Peaked (%)* *38.8*	*Notched (%)* *5.0*	*Total* *100.0*
P R interval (sec.)	0.202 ± 0.021	0.134 ± 0.023	0.192 ± 0.025	0.171 ± 0.037
Range	0.11 – 0.24	0.11 – 0.22	0.17 – 0.23	0.11 – 0.24
P duration (sec.)	0.101 ± 0.014	0.086 ± 0.013	0.103 ± 0.011	0.095 ± 0.015
Range	0.07 – 0.12	0.05 – 0.12	0.08 – 0.12	0.0[illegible] – 0.12
P R segment (sec.)	0.093 ± 0.028	0.048 ± 0.019	0.089 ± 0.026	0.075 ± 0.031
Range	0.03 – 0.16	0.01 – 0.10	0.05 – 0.13	0.01 – 0.16
Ratio P/P R segment	1.17 ± 0.30	1.[illegible]6 ± 1.69	1.16 ± 0.47	1.26 ± 1.32
Range	0.47 – 3.33	0.55 – 12.0	0.75 – 1.57	0.47 – 12.0

mal on the condition that electrocardiographic fluoroscopic and thorough clinical examination did not reveal any cardiac abnormalities

The ratio of the P/P R segment also called the Macruz index was calculated in every case in each of the three groups of P waves and its significance was evaluated

A total of 395 records was examined no distinction was made between records from males and those from females Basic measurements were taken in the groups of rounded peaked and notched P waves Correlation between the shape of the P wave and length of the P R interval was then studied in groups with the P R interval increasing by 0.02 second from 0.11 to 0.24 second Each group contained 30 observations Correlation between age of the subjects and shape of the P wave was also studied in separate age groups from under 10 years of age up to 80 years with a 10 year increase for each group The incidence of differently shaped P waves is expressed in percentages

Results

Table I reproduces the measurements in each of the three groups of P waves Comparison of the measurements in the groups with differently shaped P waves disclosed significant differences

Rounded P waves These showed the greatest incidence (56.2 per cent) the longest P wave duration was 0.101 ± 0.014 second the longest P R interval was 0.202 ± 0.021 second and the longest P R segment was 0.093 ± 0.028 second

Peaked P waves These had an incidence of 38.8 per cent The length of the duration of the P wave was the shortest 0.086 ± 0.013 second and so were the duration of the P R interval 0.134 ± 0.023 second and that of the P R segment 0.048 ± 0.019 second

Notched P waves These were observed less frequently (5 per cent) The duration of the P wave was 0.103 ± 0.011 second the P R interval was 0.192 ± 0.025 second and the P R segment measured 0.089 ± 0.026 second in length all figures were very similar to those found in the group of rounded P waves

Correlation between the shape of the P wave and the length of the P R interval (Table II) The incidence of peaked P waves had a negative and that of the rounded P waves a positive correlation with the length of the P R interval Notched P waves were observed in the zones of the longest P R interval (0.15 to 0.24 second) with almost equal frequency (6 per cent)

Correlation between age and shape of the P wave (Table III) The incidence of peaked P waves decreased and that of rounded P waves increased with advancing age Notched P waves were observed in the middle and advanced years of life with almost equal frequency

Table II. Incidence of differently shaped P waves at different lengths of the P-R interval

P-R interval (sec.)	Incidence of P wave: Peaked (%)	Rounded (%)	Notched (%)
0.11-0.12	98.5	1.5	
0.13-0.14	90.0	10.0	
0.15-0.16	48.3	45.0	6.7
0.17-0.18	15.0	75.0	10.0
0.19-0.20	3.3	90.7	6.0
0.21-0.22		94.0	6.0
0.23-0.24		94.0	6.0

Table III. Correlation between differently shaped P waves and age

Age (yr.)	Incidence of P wave: Peaked (%)	Rounded (%)	Notched (%)
0-10	100.0		
11-20	77.0	23.0	
21-30	57.0	40.0	3.0
31-40	42.0	49.5	8.5
41-50	39.0	57.5	3.5
51-60	26.0	68.0	6.0
61-70	26.0	65.5	8.0
71-80	20.0	73.0	7.0

Discussion

The normal spread of impulses is associated with a series of bioelectric currents which when algebraically summated give rise to smooth, rounded P waves. When, as often happens, summation is not so perfect, the P wave becomes peaked or shows tiny notches (Wiggers[4]). The influence of autonomic nerves on the shape of the P wave was demonstrated experimentally by Rothberger and Winterberg,—increase of the vagal tone produced rounding and decreased height, increase of the sympathetic tone a peaking and increased height of the P wave. The influence of electrolytes on the shape of the P wave has also been established both experimentally and clinically. Weller and associates[6] and Surawicz and Lepeschkin[7] have observed tall peaked P waves in cases of hypopotassemia, whereas in cases of hyperpotassemia there was a decrease in the height of the P wave even to the extent of suppression. Factors which control the morphogenesis of the P wave are multiple and still imperfectly understood.

The two basic morphologic variations of the P wave are peaked and rounded shapes. P waves of these two configurations differ from each other not only in their shape but also in their definite sizes and in their correlations.

Peaked P waves are generally taller and of shorter duration than rounded P waves. The average height of peaked P waves in Lead II measured 1.45 ± 0.52 mm. and the average duration was 0.086 ± 0.013 second. Rounded P waves were an average height of 1.16 ± 0.37 mm. (−20 per cent) and had an average duration of 0.109 ± 0.14 second (+27 per cent). These differences are not incidental but *basic* and correspond to a different structure. As far as the duration is concerned, the standard error of the mean (S.E.M.) duration of the peaked P wave expressed by the formula $\sqrt{\frac{\Sigma(\delta^2)}{n(n-1)}}$ measured ± 0.001 second, so that the limit of variation caused by simple chance equals 3 S.E.M., i.e., ± 0.003 second. The difference between the average durations of peaked and rounded P waves amounted to 0.022 second, equaling 22 standard errors, and is therefore statistically significant. Furthermore, the average length of the P-R interval in cases of peaked P waves measured 0.134 second, whereas that in cases of rounded P waves amounted to 0.202 second, i.e., 50 per cent longer. The P-R segment was noticeably shorter in cases of peaked P waves, averaging 0.048 second, whereas that in cases of rounded P waves exhibited an average length of 0.930 second, indicating an increase of 91 per cent.

Peaked and rounded P waves had a negative correlation with age and with the length of the P-R interval. Peaked P waves are more common in youth and decrease in frequency with advancing age. Rounded P waves are infrequent in youth and more common in the aged.

Again peaked P waves are more frequently associated with a short P R interval and rounded P waves with a prolonged P R interval Thus the incidence of peaked P waves in the group with the shortest P R interval from 0 11 to 0 12 second was 98 5 per cent and that of rounded P waves was 1 5 per cent This proportion was inverted in the group with the longest P R interval from 0 23 to 0 24 second in which peaked P waves were absent and rounded P waves showed an incidence of 94 0 per cent

Notched P waves in their morphologic structure and behavior resembled the rounded P waves

Morphologically the normal P R interval representing the duration of the passage of the excitation wave from the sinus node to the ventricular muscle is composed of two sections the P wave that represents the spread of activation through the auricular muscle and the P R segment that indicates the delay of stimulus caused by the auriculoventricular node The functional state of the conducting system depends on various factors e g blood supply autonomic nervous control (especially intensity of the vagal tone) adrenocortical hormones (Lown et al [8]) etc

There is some difference of opinion with regard to the upper limit of the normal P R interval Most authorities consider it to be as long as 0 20 second (Wilson [9] White Goldberger [11] Lusada Scherf and Boyd[13]) Averill and Lamb[14] define any A V conduction over 0 21 second as first degree A V block However it is generally accepted that the normal P R interval may occasionally be longer than 0 20 second Ferguson and O Connel[15] found in over 1 0 per cent of the electrocardiograms of 1 812 healthy young men a P R interval which was longer than 0 20 second and Hall Stewart and Manning[1] made the same finding in nearly 2 per cent of 2 000 apparently healthy young men In the electrocardiograms of 1 000 aviators Graybiel and associates[4] observed P R intervals which lasted 0 21 second in 4 cases 0 22 second in 8 cases and 0 24 0 25 0 26 and 0 28 second in 1 case each Therefore our upper limit of 0 24 second for the normal P R interval can be considered physiologic

As already stated the length of the P R interval is correlated with the shape of the P wave—peaked P waves prevail with short P R intervals and rounded and notched P waves with prolonged P R intervals This correlation can be explained satisfactorily by invoking the influence of autonomic nervous tone on the heart muscle

Macruz and associates [17] elaborating their pathophysiologic findings correlated the duration of the P wave with the corresponding P R segment as an index of atrial enlargement They found that the ratio of P/P R segment varies in normal subjects from 1 0 to 1 6 We have investigated this particular problem using the present observations and found that the total average (1 26 ± 1 32) as much as the averages of the differently shaped P waves (rounded 1 17 ± 0 30 notched 1 16 ± 0 47 peaked 1 76 ± 1 69) agreed *with the above stated range of the mean* ratio However in this group of normal subjects the ranges observed were so wide (0 47 to 12 0) that clinical use of the ratio for the electrocardiographic detection of atrial enlargement was negligible Pipberger and Tanenbaum [5] also found in 133 healthy subjects that the ranges of this ratio were equally wide (0 97 to 10 17) On the other hand Soloff and Zatuchni determining the volume of the atria by biplane stereoscopic venous angiography *could not find any significant correlation* between the ratio of P P R segment and atrial enlargement Therefore it appears that the clinical value of the ratio of Macruz is highly questionable

Summary

1 P waves may exhibit different shapes sizes and also correlations

2 Peaked P waves are on an average taller and of shorter duration than rounded P waves They are associated with a short P R interval and are found in younger age groups Rounded P waves are found with greater frequency in the older age groups and are associated with a prolonged P R interval

3 Notched P waves behave as round atrial waves

4 Correlations between the
P wave and the length

interval are explained by the intervention of autonomic nerves especially by differences in the vagal tone

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Arterial embolization in relation to mitral valvuloplasty

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Peripheral arterial embolization is a potential hazard throughout the life span of patients with mitral valvular disease, particularly those who are in atrial fibrillation. The knowledge of this hazard, with the possibility of death or permanent paralysis occurring at any time, is a sword of Damocles over the heads of patients with rheumatic heart disease and especially those who have already had one embolus. A number of different forms of therapy have been advocated to prevent such emboli, which ordinarily arise from thrombi in the left atria. Two of these measures have been the conversion of the atrial fibrillation to sinus rhythm and the long-term administration of anticoagulant agents to patients in atrial fibrillation who have had one or more emboli. The first method is not widely used because of the potential danger of dislodging an embolus at the time of conversion, the hazards inherent in quinidine therapy, and the difficulty in restoring normal rhythm in these patients, for the majority will again revert to atrial fibrillation. The method of long-term administration of anticoagulant drugs obviously has inherent difficulties in the regulation of this condition, and there is a risk of bleeding. However, there is evidence which suggests that there was a decrease in the occurrence of emboli in patients who were successfully carried on these drugs.

A third method of prophylaxis is by cardiac operation. Originally, amputation of the left atrial appendage was advocated to diminish the area in which the formation of a thrombus might take place, but since mitral valvuloplasty was shown to be a reasonably safe and effective procedure in patients with mitral stenosis and since less than half of the atrial clots are confined to the appendix, simple appendectomy has been largely abandoned in favor of mitral valvuloplasty, which includes varying degrees of amputation of the auricular appendage. We have presented evidence[3] that such operation for mitral stenosis does indeed exert a protective effect against the formation of emboli later on. Others with extensive experience in mitral valve operation have reported similar beneficial results.[illegible] Recently, however, two papers[11] were presented before the American Heart Association which cast some doubt on the usefulness of mitral valve operations in preventing the formation of emboli and emphasized the hazard of operative embolization. The purpose of this article is to extend our previous report by presenting in greater detail the results in a larger number of patients followed up for a longer period of time.

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No attempt will be made to discuss all of the aspects of the formation of arterial emboli in patients with rheumatic heart disease. A recent article by Askey and Bernstein summarized the current thinking in this regard and much of the relevant literature. *Reference is made to this article* and to Askey's monograph *Systemic Arterial Embolization* for discussion of aspects of the problem other than those related to mitral valvuloplasty.

The present statistics are based on a follow-up study of the first 1,500 patients with predominant mitral stenosis who were operated upon by Harken and his associates by means of closed valvuloplasty. Follow-up statistics on the first 1,000 patients of this group have already been reported, as has our classification,[10] which roughly corresponds to that of the American Heart Association. No patient was without symptoms (Group I). There were 30 patients in Group II, those with mild and static symptoms. The few patients who were operated upon because of previous emboli and who otherwise had no symptoms were placed in this group. The 1,123 patients in Group III were those with progressive symptoms, mostly pulmonary. There were 347 patients in Group IV which was composed of cardiac invalids.

Operative embolization

For the purpose of this discussion, operative embolization is defined as a peripheral embolus which occurred at the time of the mitral valvuloplasty or while the patient was still hospitalized postoperatively. Virtually all of the 89 embolic phenomena occurred in the operating room. Only 13 occurred more than 12 hours after operation, 7 within 72 hours and 6 from 4 to 21 days after operation. Of these 13 emboli, 7 occurred in the patients of Group III and 4 in patients who were in normal rhythm.

The incidence of operative emboli is indicated in Table I. As we reported previously,[14] embolization occurred in the first 100 patients more frequently than in patients who were operated upon subsequently, but there has been no significant trend since that point. Emboli were formed more often in the patients of Group IV than in those in Groups II and III, and occurred twice as frequently in the patients of Groups II and III who were fibrillating as in those in normal rhythm. This difference with rhythm was not apparent in the patients of Group IV, the vast majority of whom were in atrial fibrillation. *Patients who had had emboli* preoperatively had a greater incidence of operative embolization than did those who had never had such documented attacks. All of these differences are statistically significant ($p < 0.01$). Eleven of the 49 emboli in the patients of Group III were fatal (23 per cent), and 27 of the 40 in the patients of Group IV (67 per cent). Operative embolization accounted for about a third of the deaths during operation in both Groups III and IV. The over-all operative mortality in the patients of Groups II and III was 2.7 per cent, and in the patients of Group IV it was 22.8 per cent. This includes the much higher mortality in the operations carried out early in the series, which we have commented on.[3,4] Excluding deaths related to operative embolization, the death rates were reduced to 1.7 and 15.0 per cent, respectively. The experience of others is similar to ours and has been analyzed by Askey and Bernstein.

Although most emboli came from a dislodged thrombus in the atrium or atrial appendage, another source was fragments which were splintered off at the time of fracture of a calcified valve. It was impossible to obtain accurate figures on the incidence of this latter hazard because patients with heavily calcified valves frequently were severely ill, in atrial fibrillation, and had mural thrombi in the atrium.

The prevention of thrombi becoming emboli has been accomplished largely by the avoidance of areas in which thrombi were present, by minimal atrial manipulation, by freely flushing the atrium at the time of the incision of this structure (before the finger is inserted), and by recognizing and carefully sucking out the thrombi from the atrial appendage before the atrial clamp is released. At one time it was thought that occlusion of the head vessels, as advocated by Bailey and associates,[15] might diminish the likelihood of embolization, and this was carried out in many of the first 200 or 300 patients

It did not however materially diminish the incidence of embolization and the cerebral anoxia due to the occlusion of head vessels may have had a deleterious effect. Therefore this was abandoned except in patients who had heavily calcified valves and in whom fracture had to be carried out through the calcified area.

Other authors have suggested additional methods whereby the risk of embolization may be minimized. Bailey and Morse[1] have argued that an approach through the right side diminished the likelihood of embolization because the entry to the left atrium is not through the left atrial appendage which is one of the most frequent sites of the formation of thrombi. In this connection however it is well to point out that since this approach does avoid the left atrial appendage it eliminates at the same time an atrial appendectomy which may be one of the important factors in the prevention of subsequent emboli. Storm [1] has suggested that operation while the patient is under anticoagulant therapy is worth while and diminishes the hazards of embolization and Goodwin has suggestive evidence which confirms this. Although Storm's figures did not indicate an increased hazard from bleeding it is our belief that the safety of this procedure has not been established.

Preoperative embolization

Two hundred sixty patients of the group of 1 500 had had one or more well-documented attacks of arterial embolization sometime prior to operation the time varied from 1 day to many years. It was impossible to determine with accuracy how many of these patients were in atrial fibrillation at the time of the embolization or when the fibrillation developed. At the time of operation 212 patients showed atrial fibrillation and 48 were in normal rhythm.

Patients who had had one or more emboli within 8 weeks prior to the time of operation had twice as many operative emboli as did those in whom embolization occurred earlier (Table II). If the patients of Group III and Group IV are considered separately the results are not statistically significant but when the two groups are combined the results are significant by the chi-square test to the 5 per cent level. Although many of these patients were operated upon as semi-emergency cases because of showers of emboli (23 of the 96 in this group) the incidence of operative emboli was the same as in those who had had a single embolus. The differences cannot be explained on the basis of any differing complexion of the patient population in regard to group or rhythm. Within the 8 week period there was no trend in regard to the frequency of embolization. In patients operated upon more than 8 weeks after an embolus the time duration was also of no demonstrable significance (Table III).

Atrial thrombosis

Obviously the likelihood of embolization is related to the occurrence of atrial thrombosis. Whether or not an atrial thrombosis was noted by the surgeon at the time of valvuloplasty is reported in 1 246 of the 1 500 cases. It will be seen from Table IV that the incidence of such thrombi varied according to group and rhythm in the same manner as did the incidence of operative embolization namely it was higher in the patients of Group IV than in those of Group III and in the fibrillating patients of Group III when compared with those who had normal rhythm. It is of interest that thrombi were noted as frequently in patients without a history of preoperative emboli as in those who had had one or more embolization.

Although a fresh friable thrombus is more likely to be detached to form an embolus than is an old one we did not attempt to distinguish between the two in this study. Since the incidence of thrombi was not significantly different in the group operated upon within 8 weeks and the group operated upon more than 8 weeks after an embolus there probably is a greater frequency of fresh thrombi in this group.

Late postoperative emboli

Late postoperative emboli are defined as those occurring after the patient had left the hospital after mitral valvuloplasty. One thousand three hundred ninety patients survived operation and these have been followed up for periods up to 11

Table I. Incidence of operative emboli in relation to classification of patients' rhythm and the occurrence of preoperative embolization

	Number of patients	Number of operative emboli	Per cent of operative emboli
Groups II and III			
Without preoperative emboli			
Normal sinus rhythm	602	15	3
Atrial fibrillation	356	17	5
With preoperative emboli			
Normal sinus rhythm	43	4	10
Atrial fibrillation	153	13	9
Total			
Normal sinus rhythm	645	19 (3)	3
Atrial fibrillation	509	30 (8)	6
Combined	1 154	49	4
Group IV			
Without preoperative emboli			
Normal sinus rhythm	75	7	9
Atrial fibrillation	207	18	9
With preoperative emboli			
Normal sinus rhythm	5	1	20
Atrial fibrillation	59	14	24
Total			
Normal sinus rhythm	80	8 (3)	10
Atrial fibrillation	266	32 (24)	12
Combined	346	40	12

( ) Fatal emboli

Table II. Incidence of operative embolization in patients who had emboli within 8 weeks before operation versus those who had earlier emboli

Group	Preoperative emboli: Within 8 weeks before operation			More than 8 weeks before operation		
	Number of patients	Number of operative emboli	Per cent of operative emboli	Number of patients	Number of operative emboli	Per cent of operative emboli
II and III	77	10	13	119	7	6
IV	19	7	37	45	8	18
Both	96	17	18	164	15	9

*p [illegible] = 0.05

by annual questionnaires, by personal examination in many instances, and by additional information from the patient, his doctor, or his hospital as described elsewhere. Thirty-eight patients have had definite peripheral emboli which occurred after they left the hospital after the mitral valvuloplasty. Three of these patients had two emboli. There were 25 cerebral vascular accidents and 16 emboli to major

arteries elsewhere in the body. Seven of the episodes of embolism were fatal. Twenty-seven of the patients were classified in Group III prior to their operation and 11 in Group IV. This proportion between the two groups is similar to that of the entire group of 1,500. In 12 patients who were in normal rhythm at the time of operation, atrial fibrillation developed later. Four patients were in normal sinus rhythm at the time of operation and we have no definite knowledge that their rhythm changed subsequently. Of this group of 38 patients, 6 had had preoperative emboli and 5 had had operative emboli. There is no evidence that postoperative embolization developed in patients who were doing poorly or had undergone an inadequate valvuloplasty because almost all of the patients had what was considered to be an adequate operation at the time it was performed. At their annual follow-up examination immediately prior to the occurrence of the peripheral embolus, 23 of the 38 patients had been classified as moderately to markedly improved in their over-all cardiac status. Three had been classified as slightly improved and 3 as unchanged as the result of the operation. Eight developed their peripheral emboli within the first year before the first annual follow-up examination and we do not have accurate reports of their cardiac status at this time. In one patient who had been operated upon more than 1 year before there was

Table III. Incidence of operative emboli in patients with preoperative emboli in relation to time of occurrence

Time of emboli before operation	Groups II and III			Group IV		
	Number of patients	Number of operative emboli	Per cent of operative emboli	Number of patients	Number of operative emboli	Per cent of operative emboli
0-8 wk.	77	10	13	19	7	37
9–16 wk.	17	1	6	3	0	0
17-25 wk.	18	1	6	2	0	0
26–52 wk.	18	2	11	5	1	20
1-2 yr.	25	1	4	15	3	20
2 yr. or more	41	2	5	20	4	20
Total	196	17	9	64	15	23

Table IV. Incidence of atrial thrombosis in relation to severity of disease, rhythm, and the occurrence of preoperative emboli

Number of patients with preoperative emboli	Groups II and III				Group IV			
	Normal rhythm		Atrial fibrillation		Normal rhythm		Atrial fibrillation	
	Total number	Per cent with thrombi	Total number	Per cent with thrombi	Total number	Per cent with thrombi	Total number	Per cent with thrombi
Absent	4 1	4	295	57	55	16	1 8	3
Present	4	10	142	1		80	58	74
(Preoperative emboli within 8 wk.)	(1	(6)	(52)	(36)	(2)	(100)	(13)	(61)*

no follow up examination. As a whole, the improvement status of these patients was about the same as that for the entire group of 1,500 patients.

The emboli occurred from 1 month to 7 years after the operation, and there was a fairly constant scatter throughout this period. Twenty-two incidences of embolic episodes occurred between 1 and 4 years postoperatively, with the maximum between 2 and 3 years when there were 12. Six years is the mean follow-up examination period for this group of 1,390 survivors. Obviously, all 1,390 patients have not been followed up from operation to the present time. There have been 160 late deaths, 7 in which late peripheral embolization played a role. One hundred twenty-seven patients had had a second cardiac operation because of recurrent symptoms. Thirty have been lost from the series after varying periods of follow-up. Sixty-three are delinquent in their follow-up examination for periods which vary from a few months to a year. The other 992 have been followed up to the current anniversary of their operation. It is obvious that those who died, those who were reoperated upon, and those who are delinquent were followed up for varying periods of time after operation. It is difficult, therefore, to estimate the follow-up period in patient years, but it lies somewhere between the 992 patients who are currently being followed up and the total 1,390. Therefore, the incidence of embolization in the group as a whole would fall somewhere between 0.46 and 0.64 per cent per patient per year.

All patients who suffered from cerebral vascular accidents were classified as having had them because of cerebral emboli. Inasmuch as the average age of the patients who had late peripheral embolization was 45 years at the time of operation, it is possible that some of these patients had cerebral vascular accidents as a result of thrombosis or hemorrhage. In addition, in the cases under discussion, 2 patients were strongly suspected of having subacute bacterial endocarditis at the time at which the embolization took place, and a third patient had a fatal cerebral embolus 2 days after catheterization of the left side of the heart.

Anticoagulant therapy

Fifty-eight of the 96 patients who had had preoperative emboli within 8 weeks of operation had been on anticoagulant therapy. The type and extent of such therapy varied greatly, and in many cases was clearly inadequate. No beneficial effect of such treatment was demonstrable in preventing operative emboli. There was also no clear evidence that atrial thrombosis was diminished in patients who received anticoagulant drugs, although the suggestively lower incidence of atrial thrombosis in patients who had had a preoperative embolus within 8 weeks of operation as compared to others (Table IV) may reflect the greater use of such drugs in those patients.

The results of anticoagulant therapy are not presented in detail since a fair evaluation of such prophylactic therapy cannot be made from our data. Except in very rare instances, anticoagulant drugs were not given after operation, either early or late.

Discussion

The purpose of this study has been to define the conditions under which peripheral embolization takes place in patients with mitral valvular disease in relation to mitral valvuloplasty. The incidence of clear-cut preoperative embolization in this group was 17 per cent; other authors have reported a somewhat greater incidence. The difference may be due to the severity of our criteria of definition, for we included only patients who had unquestioned emboli.

Operative embolization remains an inherent risk of the procedure and is a major factor in the operative mortality. It is clear that there are certain conditions which modify the likelihood of embolization at the time of operation, quite aside from any special techniques that may be aimed at avoiding them. The presence of atrial fibrillation, increasing severity of heart disease, and the occurrence of preoperative embolization all heighten the risk. This has been shown by others as well as ourselves. Undoubtedly, the existence of heavy calcification of the mitral valve also increases the risk of calcific emboli, but this has not been analyzed in

the current study All of the conditions that increase the risk of operative emboli zation also contribute to the severity of heart disease as a whole and are in them selves indications for cardiac operation It is impossible therefore to define the risk to a patient of a possible embolus at the time of operation except in terms of the general condition of that patient In the abstract of a presentation by Taber and Lam[11] for instance there is no men tion of the severity of disability or of the classification of the patients It is sug gested in this report that fibrillation itself is a bad thing to have in relation to em bolization Whereas this is undoubtedly true it is equally true that most patients who are seriously disabled are also in atrial fibrillation Other factors leading to the severity of their heart disease must be considered and defined

Our findings suggest that embolization within 8 weeks before operation carries a higher risk of operative embolism than if such preoperative embolus had occurred earlier presumably because it is more likely that a friable clot is present in the atrium

Our present findings confirm our previ ous reports in respect to the protective value of mitral valve operation against future embolization With the passage of time and with the experience of an in creasing number of patients the annual incidence of such embolization has not tended to increase It has not been our practice to attempt to convert patients in chronic fibrillation to sinus rhythm except in rare instances In our earlier follow up study[3] it was shown that the incidence of fibrillation in patients a num ber of years later was the same as at the time of operation the few patients who had reverted to normal rhythm about balanced the number who developed atrial fibrillation postoperatively Since two of the factors that are undoubtedly responsi ble for protection against late peripheral embolization are the reduction of stasis in the left atrium by adequate valvulo-plasty and amputation of the left atrial appendage it is reasonable to believe that patients in whom these two measures have not been accomplished would be more likely to develop peripheral emboli zation In our experience we could not demonstrate any relationship between an inadequate valvuloplasty and the occur rence of late emboli It must be recognized however that an adequate operation by 1952 standards may be far from ade quate when judged by current techniques Virtually complete atrial appendectomy was carried out routinely later on in the series

Almost all of the patients under discus sion had symptoms of cardiac disability and one of the prime indications for oper ation was the evidence of high grade mitral stenosis which produced symptoms which could be and usually were relieved by such operation Therefore any pro tective effect against embolization was in many of these patients considered to be an added dividend rather than the prime indication for operation There was a handful of patients in whom the sole indi cation for operation was the existence of previous emboli The decision in favor of operation is easy if there is a clear-cut reason for mitral valvuloplasty on the basis of cardiac disability alone We have discussed such indications elsewhere It is important to appreciate however that patients without severe mitral stenosis who fibrillate and who may develop emboli may represent a somewhat different type of patient than the usual one who fibrillates late in the course of the disease Although significant mitral stenosis may exist with out symptoms it is nevertheless a fact that in many of the patients in this group the mitral stenosis is mild and there is little stasis in the left atrium In these patients other factors may be present which result in the development of fibril lation and in a tendency to the formation of thrombi such as a greater than usual degree of atrial endocarditis and myo carditis with scarring or some peculiarity in their clotting mechanism Hence one cannot with complete assurance translate all statistics that have been reported on the protective effect of mitral valvulo plasty against embolization to patients without symptoms but with lesser degrees of mitral stenosis This is particularly true of patients in the older age group who often develop symptoms and have fibril lation precipitated by degenerative

of atherosclerosis superimposed on a moderate amount of rheumatic heart disease.

The critical question is: Should mitral valvuloplasty be recommended in all patients with mitral valvular disease who have had an embolus or indeed in all patients with mitral valvular disease who are fibrillating? Or can one define limiting criteria which can be applied in the selection of patients who are suitable for operation?

Patients with mitral stenosis who are most likely to develop emboli are those who are fibrillating (75 or more per cent) and over 40 years of age. The embolus may occur promptly with the onset of fibrillation or be delayed for many years.[4] The probability of a patient developing an embolus is not known exactly. Bannister found that 22 of 105 patients with moderate mitral stenosis followed up for an average period of 4½ years developed peripheral emboli. In Olesen's series of 271 patients with mitral stenosis 75 developed peripheral emboli (27 per cent). Most of these patients were over 45 years of age, were in a late stage of their disease, and 85 per cent were fibrillating. Twenty-three per cent of Wilson and Greenwood's series[7] of patients with mitral valvular disease developed emboli.

Askey has estimated that 25 to 30 per cent of the patients with mitral valvular disease die as the result of emboli. These emboli occur more frequently in patients with cardiac disability and failure but there is a substantial percentage in whom this disaster is the first important cardiac symptom.

The likelihood that a patient who has survived an embolus will have a second one is excellent. Daley and associates[9] found that about a third of their group of 194 patients who had peripheral emboli developed one or more recurrences, and about a third of the recurrences were within 1 month. They found that 12 per cent died as the result of their first embolus and in an additional 28 per cent death resulted from the recurrences. In our series of 260 patients with preoperative emboli there were 16 (6 per cent) who developed a second embolus within 8 weeks. Our series may well have been slanted in favor of patients with multiple emboli within a short period because such patients would have been more likely to be referred for operation.

Although the risk of operative embolization is increased in patients who are fibrillating, who have had previous emboli, and who have more advanced disease, the risk of spontaneous embolization is also increased in these same patients if they are not operated upon. Similarly, the increased risk of operation within 8 weeks of an embolus is about balanced by the possibility that the patient will have recurrent spontaneous emboli.

When all considerations are taken into account, there is a strong indication for mitral valve operation in all patients who have had a peripheral embolus, even without significant symptoms of cardiac disability, as a protection against future emboli. Although the argument for prompt operation is, in general, at least as strong as that in favor of delaying the operation for several weeks, each patient must be considered on his individual merits. Consideration must be given to such factors as the general condition of the patient, the presence of treatable heart failure, and the risk of aggravating brain damage if operation is carried out too soon after a cerebral embolus, as well as other factors.

At the present time we do not have evidence indicating that patients in fibrillation but without symptoms who have not suffered an embolus should routinely undergo valvuloplasty. Such patients should receive careful study and close medical follow-up, and in many of these added indications pointing toward surgical intervention will develop soon.

Most of our patients did not have adequate treatment with anticoagulant drugs. Although an anticoagulant drug given in a routine manner for a short period may not greatly influence the likelihood of an operative embolus, it is possible that it will diminish the possibility of repeated emboli occurring in the period before operation. Indeed, the reported studies[1] on the prolonged use of anticoagulant drugs would suggest that this is so. In the light of our present knowledge it would seem advisable to administer them from the time of an embolus until mitral valvuloplasty is carried out. Whether or not

they should be continued during the operative period is still a moot point on which this study throws no light

Since the incidence of emboli occurring after the immediate surgical period is so low it is our opinion that the risk of routine administration of anticoagulant agents at this time is greater than the possible benefit Very few of the patients were on long term anticoagulant therapy after the operation and we have not recommended this routinely because of the low incidence of late embolization

Summary

The present study is based on our experience of peripheral arterial embolization in 1 500 consecutive patients with predominant mitral stenosis who underwent mitral valvuloplasty The purpose of this study has been to define the conditions under which such embolization takes place It has been shown that the presence of atrial fibrillation increasing severity of heart disease and the occurrence of preoperative embolization all increase the risk of operative embolization which remains an inherent risk of the procedure and is a major factor in deaths from operation

Our findings suggest that an embolus within 8 weeks of operation carries a higher risk of operative embolization than does a preoperative embolus occurring earlier

Our present findings confirm our previous reports with respect to the protective value of mitral valve operation against future embolization Late postoperative emboli have occurred in 38 patients of the entire group followed up for a mean period of 6 years an incidence of 0 46 to 0 64 per cent per patient year

Our figures show no beneficial results from preoperative anticoagulant therapy as given—for most it was given for a short period and stopped several days prior to operation—but shed no light on anticoagulant treatment given intensively for longer periods or through the period of operation The low incidence of embolization after the immediate operative period would suggest that the routine administration of anticoagulant agents is unnecessary in the postoperative period either early or late

The formation of peripheral emboli is an indication for mitral valvuloplasty in patients with mitral stenosis even without symptoms In certain patients the increased risk of operative embolization is about balanced by the increased hazard of recurrent spontaneous embolization

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Observations with the Frank system of vectorcardiography in left ventricular hypertrophy

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The accuracy of the electrocardiographic diagnosis of left ventricular hypertrophy (LVH) is an unsettled issue. Some investigators have concluded that the electrocardiogram is the most reliable clinical indicator of LVH available,[1] whereas others advise caution in the use of any current electrocardiographic standards for LVH.

Improvement in the dependability of electrocardiographic methods would be welcomed, especially when applied to early or mild examples of left ventricular overload. The employment of newer theoretically more accurate lead systems in an attempt to define LVH more precisely seems warranted.

The present study was performed to obtain spatial vectorcardiographic data with the Frank lead system in patients with LVH and to compare the results with those from a group of normal subjects studied previously.

Patients

Patients were chosen for this investigation on a clinical basis. An evident etiology for LVH was present in each case. Physical and radiographic findings confirmed the hemodynamic importance of the diseases included, and supplementary evidence was provided by right or left heart catheterization and surgical observation in several cases.

The electrocardiogram was not employed in the choice of patients, except that undoubted evidence of myocardial infarction excluded patients from study. Similar methods of selection have been employed by others.

Forty-six patients met the desired criteria. There were 7 with congenital valvular, subvalvular, or supravalvular aortic stenosis. Open-heart operation was subsequently performed in 6 of these, and a significant systolic pressure gradient across the aortic valve was measured in the seventh. Four other patients with congenital anomalies which caused left ventricular overload are listed in Table I.

There were 22 patients with rheumatic aortic valvular disease. None was believed to have hemodynamically significant mitral valvular disease. The presence of mitral disease had been excluded in clinically uncertain cases by measurements of left heart pressure and/or by angiography. All patients had the characteristic murmurs of aortic stenosis and/or regurgitation, and left ventricular overactivity or enlargement was noted on physical examination in 20. Left ventricular enlargement

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Table I. Composition by disease and age of the group of 46 patients with left ventricular hypertrophy

Type of disease	*Number*	*Age range*	*Mean age*
Congenital			
Valvular aortic stenosis	4	15-18	
Subaortic stenosis	2	18-22	
Supravalvular aortic stenosis	1	14	
Coarctation of the aorta	2	30-48	20
Tricuspid atresia with subclavian-pulmonary artery anastomosis	1	14	
Aortic medionecrosis with aortic regurgitation	1	40	
Rheumatic aortic valvular disease	22	24-64	42
Hypertension	13	35-71	52
Total	46	14-71	40

Table II. Results of analysis of Frank vectorcardiograms in 41 patients with left ventricular hypertrophy

	Horizontal	*Left sagittal*	*Frontal*
Angle of maximum QRS vector	318 degrees (256-359)	13 ± 21.7 degrees	15 ± 27.9 degrees
Angle of half area QRS vector	372 ± 17.4	24 ± 22.4	18 ± 27.0
Magnitude of maximum QRS vector	3.29 mv (1.56-8.96)	2.3 ± 0.96 mv	2.95 ± 1.40 mv
Angle of maximum T vector	99 degrees (315-16) 3 cases	167 degrees (48-252) 37 cases	124 degrees (357-230) 36 cases
Magnitude of maximum T vector	0.81 ± 0.41 mv	0.60 mv (0.23-1.18)	0.63 mv (0.29-1.75)
Maximum QRS vector-T vector angle	140 degrees (13-210)	152 degrees (32-227)	115 degrees (1-212)
Half area QRS vector-T vector angle	138 degrees (13-198)	143 degrees (9-207)	116 degrees (2-202)
Direction of inscription			
Counterclockwise	33	32	16
Clockwise	1	0	7
Linear or figure-of-eight	7	9	18
QRS loop area	3.28 units (0.32-14.22)	1.65 units (0.23-7.04)	1.48 units (0.13-9.14)
QRS loop area in 72 normal subjects	1.40 ± 0.64 unit	0.84 ± 0.53 units	0.49 units (0.06-1.50)†

*T loop was [illegible] in the other cases.
†See text for discussion.
Means ± standard deviations are listed for the LVH data which had normal distribution. The results from non-normal distributions are presented as means with the absolute ranges observed shown in parentheses below them. At the bottom of the Table means of QRS area for normal subjects are presented. Abbreviation: mv = millivolt.

was demonstrated by radiographs or left ventricular angiographs in 21.

Thirteen patients with systemic hypertension are included. All had significant disease as indicated by diastolic blood pressures above 100 recorded on most of their visits to the outpatient clinics or hospital during a period of over a year.

The ages of the various groups are shown in Table I. Two of the teen-age patients weighed less than 100 pounds and one of these was the lightest of the entire series (80 pounds).

There have been 7 deaths and LVH was verified anatomically in all, with heart weights ranging from 540 to 860 grams.

In summary, patients were chosen who had definite clinical evidence of diseases which result in LVH, and electrocardiographic signs thereof were not employed in this selection. To avoid the problem of biventricular hypertrophy, only conditions which result in pure left ventricular overwork were considered, although some patients with long standing or severe heart failure were included.

Method of study

Direct spatial vectorcardiograms (VCGs) were obtained with the lead system described by Frank. The fifth intercostal space at the sternum was used as the level for the chest electrodes, and the examination was conducted with the patient seated. The VCGs were photographed in the horizontal, left sagittal, and frontal projections with 35 millimeter film. It was later projected in an enlarging viewbox and tracings were made on paper for analysis. Standard calibration factors of 1 millivolt were similarly enlarged. The reference frame employed for angular measurements is shown in Fig. 1. The angles and magnitudes of the maximum QRS and T loop vectors were measured, as well as *the angle between them*. By means of a planimeter, the QRS loop in each projection was divided into equal half areas by a line through the isoelectric spot, as described by Pipberger. The angle of this QRS half area vector was noted, and its relationship to the T loop axis was measured.

As an empirical measurement, the total QRS loop area was determined by planimetry in the enlarged tracing of each projection. In order to compare such areas from patient to patient, an arbitrary unit of area was determined and used as follows. The length of the 1 millivolt signal in the enlarged tracings was known. This length was squared. The resulting area actually represented 1 square millivolt and is hereafter referred to as an area unit. The measured QRS loop area (by planimetry) was divided by the area of this unit to give a result in numbers of area units.

The planar mean QRS vector in each projection was determined in 21 cases in which the scalar component leads X, Y and Z were recorded. The algebraically determined net positive or negative area enclosed in the QRS complexes in each lead was determined by planimetry. Results were plotted on right angle coordinates and angles measured for each projection.

Spatial QRS-T angles were calculated for 72 normal subjects previously reported on, and for the subjects with LVH to be described.[7] The half area QRS vectors and maximum T vectors in the horizontal and frontal planes were used. Helm's trigonometric tables permit easy determination

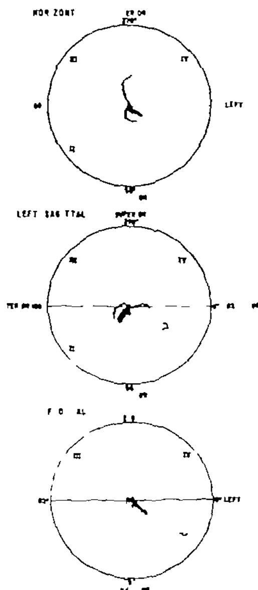


Fig. 1. Reference frame used for the angular measurements in this study. A normal VCG is shown. Time markings are 1,000 per second.

Table III Spatial QRS T angles

	Mean	Standard deviation	Range
72 Normal subjects (Frank system)	60	19 6	10–100
26 Normal subjects (Frank system)	1	22 0	———
50 Normal subjects* (SVEC III system)	56	18 8	20–10
41 Patients with LVH (this study)	126	Not calculated (non normal distribution)	35–180
1 Patients with left ventricular hypertrophy (Frank system)	91	27 0	———
15 Patients with left ventricular strain (Frank system)	141	21 0	———

[illegible] QRS-T [illegible] were calculated [illegible] been reported [illegible]

*Table IV Probability values from comparison of paired individuals from normal and LVH groups by a nonparametric method**

	Horizontal	Sagittal	Frontal
Maximum QRS vector magnitude	<0 01	<0 01	<0 01
Maximum QRS vector angle	0 48	0 03	0 01
Half-area vector angle	0 03	<0 01	<0 01
Maximum T vector magnitude	0 04	0 0	0 74
Maximum T vector angle	<0 01	<0 01	<0 01
Half area vector T angle	<0 01	<0 01	<0 01

*The W [illegible] test was applied to 19 pairs of individuals from the normal and LVH groups [illegible] The resulting probability values [illegible] vectorcardiographic differences between the two groups

of the spatial QRS T angle to the nearest 5 degrees and were employed in this study.[4]

The electronic equipment was of two types. The first part of the study was performed with a Tektronix RM 32 oscilloscope and two Type 53 54 F differential preamplifiers. Later, Type 122 preamplifiers were used with a Tektronix* 502 oscilloscope modified for vectorcardiography. This instrument has triggering and wave brightening circuits which permit photography of the QRS loop alone without the T loop or glow from the isoelectric spot. The frequency response adjustments for both instruments were set at 1 kilocycle per second for the high range and 0 06 cycle per second for the low. The beam was interrupted either 400 or 1 000 times per second, and the direction of travel was indicated by the pointed leading edges of the resulting dots.

Results

Five patients who had QRS complex durations of 0 12 second or more were considered to have left bundle branch block (LBBB). The other group of 41 patients is described in detail.

Left ventricular hypertrophy. The results from the 41 VCGs are tabulated in Table II. The frequency distribution of many of the parameters did not provide a normal distribution, and standard deviations are presented only in those instances in which a Gaussian distribution was found. The results are compared with the findings in a group of 2 people who were free of heart disease. Details of this study of normal subjects have been reported previously.[7] A given observation in the VCGs

*Tektronix, Inc., Portland, Ore

from the LVH group was classified as *abnormal* if it was outside the range of mean ± 2 standard deviations as determined in the normal subjects. A few parameters in the normal subjects had not given Gaussian distributions and in these cases the absolute ranges previously found were employed as normal limits with one exception. The measurement of QRS loop area in the frontal projection was below 1.4 units in 70 of 72 controls. (Exceptions were 2.00 and 3.71 units.) The arbitrary upper normal limit was 1.5 units.

QRS LOOP. The most consistent alteration in LVH was the large magnitude of QRS vectors. Thirty six patients had an abnormally long maximum QRS vector in at least one projection of the loop. The spatial position of the QRS loop did not necessarily present an abnormal maximum vector in all three projections but it was greater than normal in at least two projections in 31 cases.

Increased QRS magnitude was also evident in the over all large size of the loops as indicated by the QRS loop area

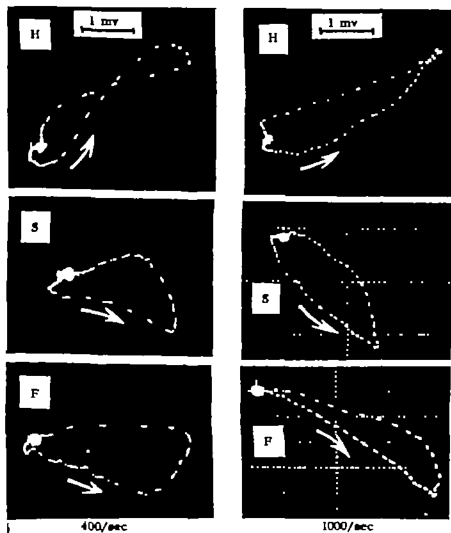


Fig. 2. VCGs from 2 patients with predominant aortic regurgitation aged 24 and 28 years. The QRS loops alone have been recorded. The maximum QRS vector is abnormally large in all projections. Initial anterior forces can be seen in the horizontal and sagittal projections in both cases. In this and subsequent illustrations H = horizontal projection; S = left sagittal projection; F = frontal projection. The frequency of time interruption is indicated at the bottom of each set of tracings.

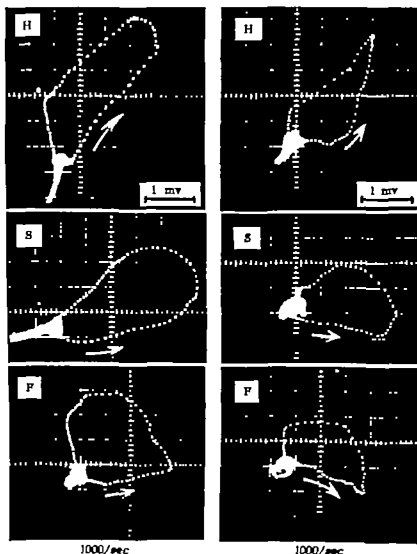


Fig. 3. *Left*, VCG from 35 year old man th aortic stenosis. Large ma m m QRS ectors are evident in the horizontal and sagittal projections. An bnormally high position of the QRS loop is seen the frontal projection. Terminal slowing of inscription suggest the presence of an element of en tricular conduction delay. The anterior and rightward location of the T loop is characteristic of cases th the fully developed findings of LVH. *Right*, VCG from an 18 year old girl th hypertrophic subaortic stenosis. The olt age bnormal ties are less marked although the position l features are similar t those of the case on the left.

measurements. Twenty nine patients had increases in QRS loop area in at least one projection. Two of the 5 patients who did not have abnormal magnitude of maximum QRS vectors had abnormally large QRS loop areas. Thus in 3 cases of the entire series the QRS size failed to exceed normal in one or more ways.

The position of the maximum QRS vector was within the normal range in all patients when viewed in the horizontal projection. In approximately one third of the patients there was an abnormally high position of the maximum or half area QRS vector in the sagittal projection and in the frontal projection in about one third of the patients. Two of the 3 patients who did not show any abnormality of QRS magnitude demonstrated abnormal elevation of the loop in the sagittal projection. Examples are shown in Figs. 2-5.

From the foregoing it is found that 40

of the 41 patients had at least one abnormality of the position or size of the QRS loop The sole exception was a hypertensive patient who had no electrocardiographic or vectorcardiographic abnormality

In all but one case there was discernible initial anterior movement of the QRS loop The magnitude of this deflection was at times small in comparison to the length of the major loop but was nonetheless identifiable (see Fig 6) Initial superiorly directed forces were consistently very small and often absent Other qualitative features of the VCGs are listed in Table II

Occasionally unusual configuration or position of the QRS loop was found and examples are shown in Figs 7 and 8

T LOOP S T VECTORS AND PLANAR QRS T ANGLES T loops were isoelectric or outside the normal ranges of angles in at least one projection in 37 cases The characteristic location of the major T axis was to the right and anteriorly More minor shifts of the T axis were present in some patients and in 4 no abnormality was discerned There were no examples of isolated T loop or QRS T angle abnormality without associated changes in the position or magnitude of the QRS loop

The presence of a rightward anteriorly directed S T vector was common in examples with the fully developed picture of LVH

Abnormalities of the maximum QRS vector–T vector angle were present in two thirds of the group thus 13 patients had normal angles This latter number decreased to 9 if the half area QRS vector–T angles were considered

Previous studies by Pipberger[4] showed a dependable similarity between the half area QRS vector angle and the true mean QRS vector angle using the SVEC III system Comparison of the half area vectors from one study with the mean planar QRS vectors from another suggested the same consistency when the Frank system was used in normal people A comparison was made between the half area QRS and the planar mean QRS vector angles in 21 of the patients in this investigation In general the values were very close The mean differences between the two measurements in these 21 VCGs were 6 1 degrees in the horizontal 7 1 degrees in the sagittal and 4 5 degrees in the frontal projection One or two larger discrepancies from 20 to 30 degrees were found in each projec

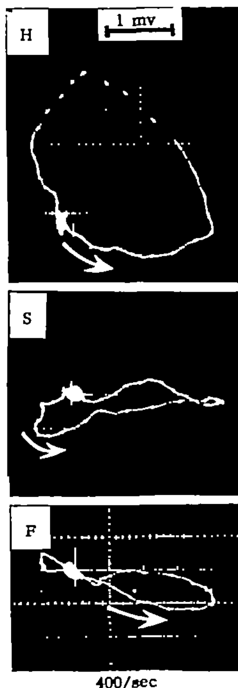


Fig 4 The QRS loops alone were recorded in this VCG from a 55 year-old man with hypertension Although the maximum QRS vector in the horizontal projection is not abnormal the QRS arrow is outside the normal range

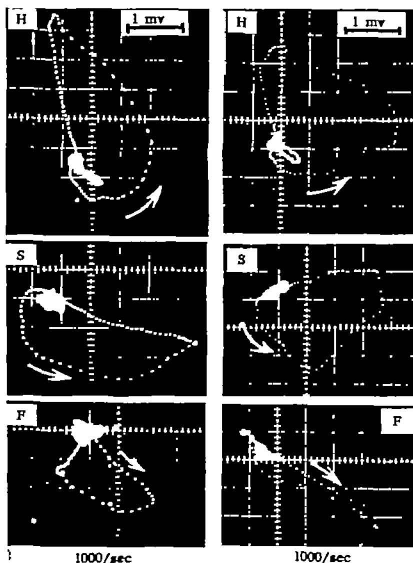


Fig. 5. *Left*, VCG from 16-year-old boy with congenital aortic stenosis and moderate pressure gradient across the aortic valve. The QRS loops are not qualitatively abnormal. However, the maximum QRS vectors and loop areas are above normal in the horizontal and sagittal projections. *Right*, Record from 1 year-old boy with congenital aortic stenosis. The QRS loop is normal in appearance but loop area is abnormally large in the horizontal and sagittal projections.

tion. The half area QRS vector angle appears to be a reasonable substitute for determination of the planar mean QRS vector angle in VCGs suspected of showing LVH.

SPATIAL QRS-T ANGLE. The spatial QRS-T angles from three groups of normal subjects who have been studied with corrected lead systems are shown in Table III. The widening of this angle in LVH is apparent as is the overlap with the normal range. All patients with LVH who had abnormal spatial QRS-T angles had planar half area QRS vector–T angles which also fell outside the normal limits.

The similarity of the spatial QRS-T angles with the Frank and SVEC III systems in studies on normal subjects is noteworthy. This and other evidence would suggest that results with these two methods will be quite similar.

COMPARISONS OF NORMAL SUBJECTS AND PATIENTS WITH LVH AS POPULATIONS. There were two problems in comparing these two

groups as population samples. First, many of the LVH measurements were not normally distributed, making standard statistical comparison invalid. Second, the normal group previously studied included very few people who were in the age ranges of 15 to 20 and 50 to 60 years. In an attempt to circumvent these problems and yet determine whether most or all of the patients with LVH did represent a different vectorcardiographic population, we compared individuals in the LVH and normal groups by nonparametric methods.

Subjects were chosen from the two groups who were within 1 year of age of each other and of the same sex. Nineteen pairs of individuals met these age and sex requirements, with ages ranging from 18 to 60 years. The Wilcoxon signed rank test[11] was used in the evaluation of seven measurements in each projection of the VCG. The probability values for the two-sided proportion are shown in Table IV. The parameters which had poor probability values were expected, i.e., the maximum QRS vector angle in the horizontal projection and results for T magnitude. The other values were satisfactorily significant.

The results are interpreted as indicating that the patients with LVH and the normal subjects were representative of vectorcardiographically different and separable populations.

ELECTROCARDIOGRAPHIC COMPARISON. Standard electrocardiograms were not obtained at the time of the vectorcardiographic examination. Electrocardiograms were recorded in 3 of the 41 patients within 3 months of the date of the VCG, and these records were analyzed in detail for evidence of LVH. The eight criteria outlined by Chou and associates were used; these include several voltage, frontal axis, and S-T, T criteria.

The electrocardiograms of 3 patients failed to meet any criteria. The VCGs of these 3 patients displayed increased QRS voltage, and two showed T abnormalities as well. In 6 other cases one electrocardiographic criterion was fulfilled in each; in 4 cases this was a delayed intrinsicoid deflection in the left precordial leads. All of these patients had multiple vectorcardiographic abnormalities, which in

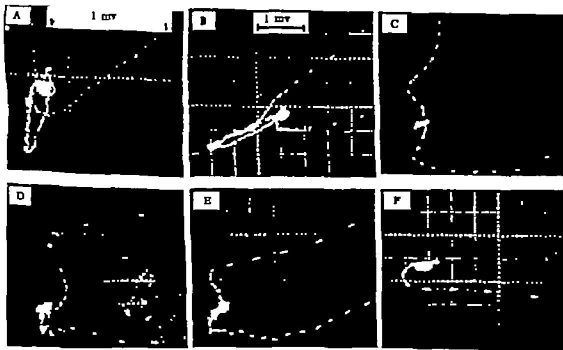


Fig. 6. Horizontal plane views of the central part of the QRS loop in 6 patients with LVH. In *A* and *B* the QRS and T complexes have been recorded. In *C* through *F* only the QRS loops are shown. Initial anterior forces are evident in each case, a finding present in 40 of 41 patients. Examples *C*, *D*, *E*, and *F* are similar in voltage calibration to *A*.

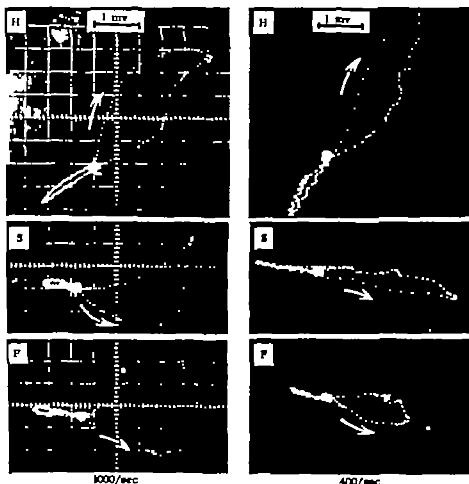


Fig. 9. Two records of left bundle branch block. *Left*, 40 year-old woman with aortic stenosis and regurgitation. *Right*, 56 year-old man with aortic stenosis. In both cases the QRS and T loops are discordant. Conduction delay is evident and an abnormal direction of inscription is seen in the horizontal projection.

It should be added that these normal VCGs were not far outside the statistically established tentative normal ranges and that diagnostic accuracy will increase markedly when magnitude values exceed the normal by more than approximately 30 per cent. In the individual VCG considerable supporting evidence for LVH will be found with associated abnormalities of T loop and QRS-T angle.

Observation of the thickness of the chest wall remains an important consideration when voltage criteria alone are employed. A striking example was seen in a man who had no heart disease, was 66 inches tall and weighed 97 pounds. His VCG demonstrated marked increases above normal in QRS loop area which could be falsely interpreted as representing LVH.

There is a possibility that a higher incidence of false positive diagnosis will be found in the subjects who are in the age range of 15 to 20 years, since the age range of subjects in the normal control group began at 19 years. Preliminary data from normal children suggest that this will not be the case, however.

Left bundle branch block. Five patients met electrocardiographic and vectorcardiographic criteria for LBBB. Four had advanced rheumatic aortic valvular disease and 1 died from coarctation of the aorta. Examples are shown in Fig. 9.

Discussion

Ideal electrocardiographic or vectorcardiographic criteria for LVH would be those with little or no overlap with the normal

population and with no resemblance to other abnormalities For this reason emphasis in this study was placed on alterations in the QRS loop with a desire to avoid the lack of specificity of QRS-T angle and T loop abnormalities These were common in our patients but it is important to note that they did not occur as isolated findings without alterations in the QRS loop A VCG which demonstrates no QRS abnormality would appear to have little chance of indicating LVH

The Frank VCG is a sensitive means of diagnosing LVH and it is suspected that additional study will prove its superiority to the standard electrocardiogram in this respect However the incidence of false positive diagnoses due to high voltage in some of the normal subjects is somewhat disappointing When several parameters are measured and a diagnosis is suspected on the basis of the observation of one abnormality some degree of false positivity seems unavoidable At present if voltage above our tentative normal range is used as a diagnostic criterion it appears that there will be a minimum chance of overdiagnosis in about 6 per cent of the people who do not have LVH This is a lower incidence of positive error than most electrocardiographic studies have claimed

The presence of initial anterior forces in all but one patient with LVH is noteworthy Tiny or absent R waves in the right and mid precordial leads of the electrocardiogram pose a difficult problem in excluding anteroseptal myocardial infarction in some patients with LVH The orthogonal VCG should prove to be of aid by demonstrating initial anterior positivity in such patients and thereby helping to exclude infarction The dependability of this sign will require proof by clinicopathologic correlations

The cases studied represented various grades of severity of physiologic abnormality Teen-age patients with systolic gradients of from 25 to 50 mm across the aortic valve are included as mild examples as well as other patients with extreme disability It appears that there is an electrical evolution of LVH which begins with changes in the magnitude and position of the QRS loop Movement of the T axis anteriorly and to the right follows and LBBB will eventually develop in some patients as the end stage electrical pattern of LVH

Finally it should be emphasized that the ranges in voltage which are described can be applied with certainty only in VCGs obtained with the Frank lead system Although observations strongly suggest close correspondence between the SVEC III and Frank methods[13,14] additional study with pathologic groups by the two methods is needed before it can be concluded that QRS magnitude data are interchangeable

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Studies of blood pressure, heart rate, and the electrocardiogram in adult twins

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The demonstration of heredity as a predisposing factor to different forms of cardiovascular disease[1] indicates a need for determining the relative importance of hereditary influence upon the variability of different physiologic processes relating to cardiac function. For this the initial problem is to determine whether measured variation in such processes has a discernible hereditary component. Studies of blood pressures in twins have been employed for this purpose,[2] and electrocardiographic patterns and heart dimensions have been compared in identical and fraternal twins.[3] In the study on twins which we are reporting here a number of different measurements of cardiac function have been taken under uniform conditions in the same adult subjects; this permits a comparative evaluation of the relative importance of genetically conditioned variability in different measurements which are used clinically to describe cardiac function.

The study sample

The 53 pairs of twins utilized in this analysis consist of 34 monozygotic (MZ) pairs (14 male and 20 female pairs) and 19 like-sex dizygotic (DZ) pairs (5 male and 14 female pairs). All subjects were over 18 years of age, with a mean age of 25.4 years for males and 29.5 years for females. In each category of sex and zygosity the age distributions were comparable, and since the analysis is based upon the differences within the pairs of twins in whom age is identical, the effect of age upon the studies is minimized. On the basis of history, physical examination, and laboratory work-up all subjects were judged to be in good general health. The methods of diagnosis of zygosity as well as the physical and socioeconomic description of the subjects have been previously presented.

Methods

The two members of each pair of twins were scheduled for simultaneous studies. In 6 instances (4 MZ and 2 DZ pairs) it was not possible to study both members of the pair of twins on the same day, but since the conditions of study were standardized and were uniform for the two members of each of these pairs, and since the differences within the pair in these individuals were not significantly dissimilar to those within the other pairs studied, they were included in the present analysis.

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The subjects came to the laboratory in a fasting state and every effort was made to maintain the basal state during the entire procedure. After a resting period of 30 minutes 4 ballistocardiograms (BCG) and simultaneous electrocardiograms (ECG) utilizing the 3 standard limb leads were taken over a period of 10 minutes. At the end of the procedure a routine 12 lead electrocardiogram was taken on each subject. Blood pressure and pulse rates were recorded at 1 minute intervals beginning 10 minutes before the first ballistocardiogram and continuing throughout the procedure. The blood pressure was determined by means of the standard arm cuff and mercury manometer utilizing the first appearance of sounds as the systolic pressure and the disappearance of the sounds as the diastolic pressure. The blood pressure reading obtained during the final 10 minutes were averaged and the average systolic and diastolic pressures were used in the statistical analysis. The heart rates used in the analysis were obtained from the ballistocardiographic and simultaneous electrocardiographic tracings. Pulse rates were also obtained from the routine 12 lead electrocardiograms and these were used in the analysis to determine any differences between those taken under strictly basal conditions and those under slightly less basal conditions. The electrocardiograms were compared for the general form of the complexes with measurements of QRS, Q T and P R intervals and heart rate being made in Lead II of the routine tracings. All of the measurements were made individually and later paired to determine intrapair differences. The diagnosis of zygosity was applied just prior to the statistical analysis.

The statistical method used is based upon a paired analysis. The average of the differences between the two members of the pairs of twins have been expressed as mean intrapair variances in which the mean intrapair variance is $\Sigma x^2/2n$ where x is the difference between the two members of a pair of twins and n is equal to the number of pairs of twins. The F distribution is used to obtain the probability level of the ratios of the different mean variances.

To permit a comparison of the mean of the differences between the two members of the pairs of twins to the mean of the differences expected to occur between two unrelated individuals in the study population mean interpair variances have been calculated. The mean interpair variances

$$s = [\Sigma x^2 - (\Sigma x)^2/n] / n-1$$

are calculated from the average of the values for the two members of each pair of twins. These variances are multiplied by two to make them comparable to the mean intrapair variances and the F distribution is used to obtain the probability level of the ratios of different mean interpair and intrapair variances. In the comparison of monozygotic and dizygotic mean intrapair variances and intrapair and interpair variances a one tail test of significance will be given when comparisons between the sexes are made a two tail test is required.

In the analysis which follows certain features which characterize data on twins are of particular importance. Monozygotic mean intrapair variances represent the average of the differences between genetically identical individuals who have had the similarity of life history and environment which this genetic relationship and common home environment impose. Dizygotic twins differ in their genetic relationships as do ordinary brothers and sisters; on the average they differ in one half of their total genetic endowment. The similarity of life history and environment in dizygotic twins in so far as these are dependent upon maternal age history of pregnancy and parity and a common home environment is comparable to that of monozygotic twins. When these influences differ excessively from those for monozygotic twins they must be presumed to relate either directly or indirectly to the genetic differences between the two members of dizygotic pairs (with the exception of particular prenatal factors which may differ for the two types of twins. However selection of pairs on the basis of health status should reduce the seriousness of the latter influences in the present data.[11] Mean interpair variances represent the average of the differences between unrelated individuals with the genetic and environmental dissimilarity which characterizes the study population.

Table I. Individual ranges, averages, and standard deviations of basal measurements*

	Males				Females			
	n	*Range*	*Mean*	*S.D.*	*n*	*Range*	*Mean*	*S.D.*
Systolic pressure (mm. Hg)	19	94–137	113.21	12.71	34	87–128	109.24	9.35
Diastolic pressure (mm. Hg)	19	64–94	77.32	7.73	34	49–91	76.41	8.85
Heart rate† (BCG) (beats/min.)	19	47–90	62.21	9.04	34	54–99	70.76	9.20
Heart rate† (ECG) (beats/min.)	19	47–84	63.58	8.96	34	55–111	72.59	13.86
P-R interval (sec.)	19	0.13–0.20	0.166	0.020	34	0.12–0.20	0.163	0.023
QRS interval (sec.)	19	0.04–0.08	0.065	0.015	34	0.04–0.10	0.061	0.019
Q-T interval (sec.)	19	0.28–0.43	0.362	0.033	34	0.28–0.44	0.367	0.039

*One individual of each pair of twins taken at random.
†Males and females differ significantly, $p < 0.01$.

Results

The ranges, means, and standard deviations of the measurements analyzed are given for males and females in Table I. These values are based upon one member of each pair of twins taken at random to provide a description of the study population. As would be anticipated in a population free of any clinically discernible condition which may adversely influence the observation, all values are within commonly defined normal limits. The mean interpair and intrapair variances for the blood pressure and heart rate, their variance ratios, and the probability levels of these ratios are presented in Table II. The MZ interpair/intrapair variance ratios for systolic, diastolic, and mean pressures are statistically significant in females but not in males. In males the MZ and DZ interpair/intrapair variance ratios for heart rate are statistically significant, but neither comparison is significant in females. These findings are consistent with the comparison of monozygotic and dizygotic intrapair variances in males and females. Whereas in males the monozygotic blood pressure variances even exceed the dizygotic variances, in females the MZ/DZ intrapair variance ratios are statistically significant for systolic pressure and mean pressure; the diastolic ratio falls short of the 5 per cent level. In females a significant component of genetic variability is measured at least for systolic and mean pressure. It appears that basal blood pressure is subject to greater environmental influence in males than in females. When the monozygotic mean intrapair variance of males and females is compared, the male variances are consistently larger than the female variances and significantly larger for systolic pressure (F ratio = 3.61, $p > 0.005$).

The sex difference in both the monozygotic and dizygotic intrapair variance ratios for heart rate (like the interpair/intrapair variance ratios) differs markedly from that in both for blood pressure. Neither the male nor the female MZ/DZ intrapair variance ratios are statistically significant for heart rate, but, unlike the situation for blood pressure, the male monozygotic intrapair variance is smaller

than that of the female and when considered with the interpair intrapair variance ratios suggests that environmental influences may be a relatively more important factor in the heart rate of females than of males

The results of the electrocardiographic studies are presented in Table III Both QRS and Q T intervals provide large and highly significant monozygotic interpair intrapair ratios Large and highly significant female MZ DZ ratios are also found which suggest a strong genetic component of variability for these two variables—stronger than for any of the other variables analyzed The comparability of the male and female monozygotic intrapair variances of the monozygotic interpair intrapair variance ratios indicate that with a larger male dizygotic sample similar findings might be anticipated for males

Heart rate and P R interval stand in marked contrast to QRS and Q T intervals both in terms of measured genetic variability and sex influence The heart rate variances given in Table III also differ rather markedly from the heart rate variances in Table II With the exception of male monozygotic interpair and female monozygotic intrapair variances the variances are larger than those calculated at the time of the electrocardiogram The ECG followed the BCG and apparently the departure from the basal conditions which prevailed at the time at which the latter was recorded influenced heart rate The differential change in heart rate suggests that there may also be a demonstrable genetic and sex influenced factor in the lability of heart rate The female monozygotic interpair heart rate variance which in Table II was slightly smaller than that observed for males is now significantly greater than male variance (F ratio = 3 41 $p > 0.025$) Both the female MZ and the female DZ interpair heart rate variances when taken at the time of the ECG are significantly greater $p > 0.025$ than when taken at the time of the BCG

From Table III it is apparent that genetic variability in the ECG pattern can be measured objectively by QRS and Q T intervals in females Presumably this would also be true in males with a larger sample of dizygotic male twins Moreover from the analysis of heart rate it is apparent that not only are the conditions of study important but that by changing the conditions of study it may be possible as well to demonstrate sex and genetically conditioned differences in heart rate lability

Interrelation of measurements

The interrelation or association between measurements is frequently of great importance In twins it is possible in some instances to examine the nature of the interrelation between measurements by a cross twin analysis By this method the correlation between measurement A and measurement B in the same individual is compared to the correlation between measurement A in one twin and measurement B in the co twin When the within individual correlation is compared to the monozygotic cross twin correlation the relative strength of the within individual mechanical and physiologic environment upon the interrelation of the two measurements can then be assessed Since the within individual environment is excluded in the cross twin correlation any correlation of measurements is the consequence of either the genetic or environmental influences or both which act similarly upon the two traits in the two different but genetically identical individuals Similar cross twin correlations with dizygotic twins make it possible to further evaluate the monozygotic cross twin correlations for the genetic and environmental basis of the observed relationships The statistic used for the cross twin analysis is the correlation coefficient When the correlation coefficient is employed particularly in small samples it is necessary to base conclusions upon the calculated probabilities rather than upon the magnitude of the correlation coefficients Evaluation of the relative sizes of different correlations should be based upon values of z[11] In view of the fact that correlations which compare a part with the whole or one measurement with another from which it is partially derived are not meaningful only certain correlations are possible with the present data For example correlations of [illegible] or diastolic pressure with mean [illegible]uld not be meaningful The

Table II Mean interpair and mean intrapair variances for monozygotic and dizygotic twins

Zygosity	Comparison	Males n	Males Variance	Males F ratio	Males p	Females n	Females Variance	Females F ratio	Females p
				Systolic Pressure					
MZ	Interpair	13	127 70			19	106 52		
	Inter Intra			1 43	>0 25			4 30	0 001
MZ	Intrapair	14	89 54			20	24 78		
	MZ DZ			0 73	<0 75			2 29	<0 05
DZ	Intrapair	5	(5 00			14	56 75		
	Intra Int			2 41	<0 25			1 91	<0 25
DZ	Interpair	4	156 50			13	108 6?		
				Diastolic Pressure					
MZ	Interpair	13	74 16			19	136 64		
	Inter Intra			1 42	>0 25			5 07	<0 001
MZ	Intrapair	14	52 11			20	26 93		
	MZ DZ			0 33	<0 75			2 14	>0 05
DZ	Intrapair	5	1 20			14	57 71		
	Intra Inter			1 60	>0 25			0 98	<0 75
DZ	Interpair	4	27 50			13	56 76		
				Mean Pressure					
MZ	Interpair	13	9 24			19	134 93		
	Inter Intra			1 42	>0 25			6 10	<0 001
MZ	Intrapair	14	55 87			20	22 11		
	MZ DZ			0 49	>0 75			2 46	>0 025
DZ	Intrapair	5	2 39			14	54 50		
	Intra Inter			3 0?	>0 10			1 12	>0 25
DZ	Interpair	4	82 8			13	61 30		
				Heart Rate					
MZ	Interpair	13	127 54			19	119 37		
	Inter Intra			4 83	<0 005			2 27	<0 05
MZ	Intrapair	14	26 43			20	52 60		
	MZ DZ			0 19	>0 9			0 98	<0 75
DZ	Intrapair	5	3 10			14	51 54		
	Intra Inter			9 22	<0 0 3			1 25	>0 25
DZ	Interpair	4	4 00			13	64 31		

The [illegible] significantly [illegible] female monozygotic [illegible] (F ratio = 3 41 p > 0 005)
The greater than (>) or less than (<) [illegible] the [illegible] by Pearson and Hartley (1956) [illegible] 0 05 0 025 0 01 0 05 0 005
MZ Monozygotic, DZ Dizygotic

Table III Electrocardiogram Mean interpair and mean intrapair variances for monozygotic and dizygotic twins

Zygosity	Comparison	Males n	Variance	F ratio	p	Females n	Variance	F ratio	p
				Heart Rate					
MZ	Interpair Inter Intra	17	88 50	2 98	>0 0	19	30 00	6 42	<0 001
MZ	Intrapair MZ DZ	13	29 65	0 29	>0 90	20	47 05	1 31	>0 25
DZ	Intrapair Intra Inter	5	8 60	20 29	<0 005	14	61 57	3 96	<0 01
DZ	Interpair	4	174 50			13	243 54		
				P R Interval					
MZ	Interpair Inter Intra	13	0 631	57	0 05	19	0 872	3 04	<0 01
MZ	Intrapair MZ DZ	14	0 246	0 78	>0 90	20	0 2 0	1 64	>0
DZ	Intrapair Intra Inter		0 0 0	5 14	>0 05	14	0 44	1 40	>0 5
DZ	Interpair	4	0 360			13	0 670		
				QRS Interval					
MZ	Interpair Inter Intra	13	0 384	7 25	<0 001	19	0 136	2 67	<0 0
MZ	Intrapair MZ DZ	14	0 053	0 38	<0 90	20	0 0	8 1	<0 001
DZ	Intrapair Intra Inter	3	0 020	18 00	<0 005	14	0 4 5	0 85	<0 7
DZ	Interpair	4	0 360			13	0 360		
				Q T Interval					
MZ	Interpair Inter Intra	13	2 184	1 00	<0 001	19	2 0	11 84	<0 001
MZ	Intrapair MZ DZ	14	0 182	0 60	<0 7	20	0 17	5 04	<0 001
DZ	Intrapair Intra Inter	5	0 110	4 18	<0 10	14	0 88	1 59	<0 25
DZ	Interpair	4	0 460			13	1 400		

F mal mono [illegible] va ianc [illegible] sign fica ly lar [illegible] th [illegible] male m [illegible] ic ian ac (F [illegible])

Table II Mean interpair and mean intrapair variances for monozygotic and dizygotic twins

Zygosity	Comparison		Males				Females		
			Variance	F ratio	p		Variance	F ratio	p
			Systolic Pressure						
MZ	Interpair	13	127 70			19	106 52		
	Inter Intra			1 43	>0 25			4 30	0 001
MZ	Intrapair	14	89 54			20	24 78		
	MZ DZ			0 73	<0 75			2 29	<0 05
DZ	Intrapair	5	65 00			14	56 75		
	Intra Inter			2 41	<0 25			1 91	<0 25
DZ	Interpair	4	156 50			13	108 62		
			Diastolic Pressure						
MZ	Interpair	13	74 16			19	136 64		
	Inter Intra			1 42	>0 25			07	<0 001
MZ	Intrapair	14	52 11			20	26 93		
	MZ DZ			0 33	<0 75			2 14	>0 05
DZ	Intrapair	5	17 20			14	57 71		
	Intra Inter			1 60	>0 5			0 98	<0 75
DZ	Interpair	4	7 50			13	56 76		
			Mean Pressure						
MZ	Interpair	13	79 24			19	134 93		
	Inter Intra			1 42	>0 2			6 10	<0 001
MZ	Intrapair	14	5 87			20	2 11		
	MZ DZ			0 49	>0 75			2 46	>0 025
DZ	Intrapair	5	2 39			14	54 50		
	Intra Inter			3 02	>0 10			1 12	>0 25
DZ	Interpair	4	8 85			13	61 30		
			Heart Rate						
MZ	Interpair	13	127 54			19	119 37		
	Inter Intra			4 83	<0 005			2 27	<0 05
MZ	Intrapair	14	26 43			20	52 60		
	MZ DZ			0 19	>0 95			0 98	<0 75
DZ	Intrapair	5	5 10			14	51 54		
	Intra Inter			9 22	<0 075			1 25	>0 25
DZ	Interpair	4	47 00			13	64 31		

*The male monozygotic intrapair ... is significantly ... than the female monozygotic intrapair variance (F ratio = 3 61 p > 0 005)

The greater than (>) or less than (<) ... is applied ... the nearest percent ... points given by Pearson and Hartley (1956) 0 5 10 0 05 0 0 5 0 01 0 005 0 001

MZ Monozygotic DZ Dizygotic

tant role in the expression of genetically conditioned variability. There was no evidence of a genetic component of variability for heart rate or pulse pressure in the present data. In comparing heart rate variances of males and females and for heart rate obtained at the time of the BCG and ECG, it appears that heart rate is more readily modified by environmental factors in females than in males and that the relative lability of heart rate may be under genetic control.

The mean monozygotic intrapair variances of males is larger than that of females for both systolic and diastolic pressure, and this difference is statistically significant in the case of systolic pressure. A similar sex difference was reported by Hines and associates[8] in a study of hypertensive vascular disease in twins. When identical twins were females the hypertensive vascular disease was of about the same degree of severity and the blood pressures were in about the same range of elevation. In contrast, when the twins were males, one twin usually had much more severe hypertensive vascular changes and had died at an earlier age than the other twin.[8] In the present study, in the case of normal blood pressures, male monozygotic twins differ more than do female monozygotic twins.

The influence of sex on blood pressure is further demonstrated by the cross-twin analysis. In female monozygotic twins the cross-twin correlation between systolic and diastolic blood pressure is statistically significant, $r = 0.550$, $p = 0.02$, whereas in males this correlation is zero. Böe and co-workers[14] have also noted that the correlation of systolic and diastolic pressure is generally better in females than in males. The cross-twin correlation employed here implies that the sex difference may actually represent modification of a genetically conditioned relationship of systolic and diastolic pressure.

These data on adult twins imply, as do family studies,[13] that genetic influences account for a relatively minor proportion of the variability observed in normal blood pressure. However, the conclusions drawn from these data on twins depart in one important respect from those derived from family studies. Pickering states that the independence of sex so far as inheritance is concerned is another simplification, for it is unnecessary to separate fathers from mothers, brothers from sisters, or sons from daughters. The evidence in twins indicates that such a separation of the sexes is necessary for the genetic interpretation of data on blood pressure. A more complete discussion is presented in a separate communication.[3]

Summary

Studies of blood pressure, heart rate, and the electrocardiogram have been analyzed for 53 pairs of twins. All subjects were over 18 years of age and judged to be in good general health on the basis of histories of health, complete medical examinations, and laboratory tests. Every effort was made to maintain the basal state during the course of the study and to assure comparability for the two members of the pairs of twins.

In a comparative analysis of the different measurements taken, a strong genetic component of variability was found in the QRS and Q-T intervals of the electrocardiogram. Systolic, diastolic, and mean pressures also gave some indication of genetic variability, but these measurements were found to be most importantly characterized by sex influences.

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Experimental and laboratory reports

Effects of isoproterenol on cardiac output and renal function in congestive heart failure

*Harold Sandler M D**
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Isoproterenol is a sympathomimetic amine that produces potent positive inotropic and chronotropic cardiac effects[1] Previous studies have shown that the peripheral vascular effects of isoproterenol differ from the marked vasoconstrictor effects of many of the other sympathomimetic amines in both man and experimental animals[2-10] Since this drug increases cardiac contractility and lowers systemic vascular resistance an increased cardiac output and lowered peripheral venous pressure regularly occur in both normal man and subjects with congestive heart failure Several investigators have observed a renal vasodilator action of intravenously infused isoproterenol in experimental animals[11] In this study the cardiovascular and renal effects of intravenously infused isoproterenol were compared in human subjects with congestive heart failure These studies have been previously reported in part in preliminary form

Methods

Twelve male subjects with heart diseases of varied etiologies were selected for study on the basis of clinical findings characteristic of congestive heart failure with edema The majority of subjects were studied on their second hospital day regardless of the state of digitalization or diuresis Diuretics were withheld on the day of study Subjects with third-degree atrioventricular heart block were excluded from the study

All tests were performed after the subjects had fasted for 10 to 12 hours To insure adequate hydration 240 c c of water were administered by mouth every 30 minutes for 2½ to 3 hours prior to the determination of renal clearances and hydration was continued during the study by administration of 100 c c of water by mouth each 30 minutes and or by intravenous infusion of 5 per cent dextrose in water at rates of 3 to 4 c c per minute for the duration of the study

Specimens of urine were collected by an indwelling catheter The bladder was emptied by injection of 10 ml of air and aspiration followed by injection of 20 ml of distilled water and then 20 ml of air with expression of any residue by appli

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Experimental and laboratory reports

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Isoproterenol is a sympathomimetic amine that produces potent positive inotropic and chronotropic cardiac effects.[1-4] Previous studies have shown that the peripheral vascular effects of isoproterenol differ from the marked vasoconstrictor effects of many of the other sympathomimetic amines in both man[illegible] and experimental animals.[illegible] Since this drug increases cardiac contractility and lowers systemic vascular resistance, an increased cardiac output and lowered peripheral venous pressure regularly occur in both normal man and subjects with congestive heart failure. Several investigators have observed a renal vasodilator action of intravenously infused isoproterenol in experimental animals.[illegible] In this study the cardiovascular and renal effects of intravenously infused isoproterenol were compared in human subjects with congestive heart failure. These studies have been previously reported in part in preliminary form.[illegible]

Methods

Twelve male subjects with heart diseases of varied etiologies were selected for study on the basis of clinical findings characteristic of congestive heart failure with edema. The majority of subjects were studied on their second hospital day regardless of the state of digitalization or diuresis. Diuretics were withheld on the day of study. Subjects with third-degree atrioventricular heart block were excluded from the study.

All tests were performed after the subjects had fasted for 10 to 12 hours. To insure adequate hydration, 240 c.c. of water were administered by mouth every 30 minutes for 2½ to 3 hours prior to the determination of renal clearances and hydration was continued during the study by administration of 100 c.c. of water by mouth each 30 minutes and/or by intravenous infusion of 5 per cent dextrose in water at rates of 3 to 4 c.c. per minute for the duration of the study.

Specimens of urine were collected by an indwelling catheter. The bladder was emptied by injection of 10 ml. of air and aspiration, followed by injection of 20 ml. of distilled water and then 20 ml. of air with expression of any residue by [illegible]

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cation of suprapubic pressure The bladder washout procedure did not exceed 1½ minutes

After a blank 15 minute collection period a priming dose of 20 to 30 ml of 10 per cent inulin was given over a 5 minute interval followed by administration of a mixture of para aminohippurate (PAH) and inulin by a constant infusion pump to maintain blood levels of 10 to 20 mg per cent inulin and 1 to 3 mg per cent PAH[15,16] Fifty five minutes were allowed for equilibration Control periods consisted of three 15 minute collection periods followed by two or three 15 minute collection periods during intravenous infusion of isoproterenol at rates of 1 to 4 γ per minute This rate of infusion was unassociated with subjective symptoms except in one subject who experienced anginal pain and a sinus tachycardia of 140/min which required discontinuance of the study

Table I

Subject and diagnosis	*CI (L/min/M²)*		*RBF (c.c./min/M²)*		*Mean systemic BP (mm Hg)*	
	Control	*Isuprel*	*Control*	*Isuprel*	*Control*	*Isuprel*
R C Syphilitic HD no digitalis	1 88	3 49	123	148	94	94
B K IMH on digitalis	1 46	2 30	80	129	118	103
F D IMH on digitalis	1 22	2 34	208	216	90	88
J M ASHD on digitalis	2 43	3 38	238	293	97	92
E G ASHD on digitalis	1 78	2 83	557	585	112	101
N K H and ASHD no digitalis	1 86	2 11	136	141	156	146
M B ASHD on digitalis	2 11	2 37	88	93	87	84
E B H and ASHD no digitalis	3 91	4 22	127	154	137	143
L H RHD on digitalis	1 42	1 94	80	94	74	71
S N RHD on digitalis	2 29	4 98	267	327	17	162
J S HCVD on digitalis	1 50	2 30	145	149	123	124
H J ASHD on digitalis	1 66	3 25	216	322	105	110
Mean	1 96	2 96	189	221	114	110
s	73	93	132	142	30	28
t	4 91		3 665		2 12	
p	< 01		< 01		< 05	

IMH Idiopathic myocardial hypertrophy ASHD Arteriosclerotic heart disease HCVD Hypertensive cardiovascular disease BP Blood pressure VP Venous pressure RBF Renal blood flow

$$RBF = \frac{ERPF\ cc/min}{1 - \frac{0.96 \times Hct}{100}}$$

Analyses for inulin were performed by the method of Handelsman and Drablin.[7] PAH was determined by the method of Bratton and Marshall as modified by Smith and co-workers.[11] Determinations of sodium were made by a Baird internal standard flame photometer. Piperocaine was used throughout for local anesthesia to avoid interference with determinations of PAH. All renal clearances were corrected for body surface area.

Peripheral venous and brachial intra-arterial pressures were determined by strain gauges and recorded on a multichannel recorder. Mean pressures were obtained by electrical integration. Cardiac outputs were determined from dye-dilution curves after peripheral injection of Evans blue dye as previously described.[4] Vascular resistance was calculated from the difference of systemic arterial and venous pressures and systemic and renal blood flows.[13]

Mean systemic VP (mm Hg)		*SVR (dynes sec cm⁻⁵ × 10³)*		*RVR (dynes sec cm⁻⁵ × 10³)*		*RVR/SVR*	
Control	*Isupred*	*Control*	*Isupred*	*Control*	*Isupred*	*Control*	*Isupred*
14	12	1 94	1 05	29 1	24 7	15 0	23 6
16	15	2 74	1 50	49 8	26 7	18 2	17 8
13	9	2 85	1 53	17 1	16 5	6 0	10 8
5	4	1 76	1 21	17 9	14 0	10 2	11 6
15	14	2 64	1 50	8 4	7 2	3 2	4 8
15	13	3 65	2 82	47 5	43 0	13 1	15 3
17	17	1 56	1 33	37 3	32 1	23 9	24 2
20	14	1 61	1 5	51 4	42 5	30 4	27 5
15	15	1 81	1 25	32 3	25 7	17 8	20 7
11	9	3 29	1 44	28 2	21 9	8 6	13 2
—	—	—	—	—	—	10 1	19 2
—	—	—	—	—	—	7 7	10 2
14	12	2 39	1 5	31 9	25 4	13 7	16 7
4	4	75	49	14 8	11 6	7 86	6 69
3 40 < 01		5 129 < 01		3 25 < 01		2 91 < 02	

RHD Rheum[illegible] heart disease CI Ca[illegible] SVR [illegible] vascular [illegible] RVR R[illegible] vascular [illegible]

Results

Type of heart disease state of digitalization and respective hemodynamic data of individual cases at the time of determination of renal clearances are presented in Table I The observations of renal function during infusion of isoproterenol in subjects with congestive heart failure are listed in Table II Cardiac output and renal function during the control periods were consistent with the findings of other observers for subjects with congestive heart failure[22 24] The control cardiac indices were low except in Subject E B and effective renal plasma flows (ERPF) were low for all subjects except E G Control venous pressure was increased in all subjects except in J M The control filtration fraction (FF) was elevated in all cases In those subjects in whom concentrations of urine and serum sodium were determined control sodium excretion was markedly depressed except in Subject R C

During infusion of the drug all subjects had an increase in cardiac index and renal blood flow to or toward normal as illus

Table II

Subject and rate of infusion	GFR (c/m /1 73 M)		ERPF (/min /1 73 M)		FF (%)	
	Mean control	Mean isoprot	Mean control	Mean isoprot	Mean control	Mean isoprot
R C 2 /min	67 6	74 1	112 3	135 7	55 7	54 7
B K 1 8 /min	40 1	44 2	69 6	111 9	58 3	39 1
F D 1 6 /min	81 2	9 9	197 5	205 2	41 8	39 0
J M 1 5 /min	90 /	87 0	242 5	295 6	37 5	29 4
F C 2 4 /min	149 7	141 8	612 1	642 3	24 4	22 1
N K 1 γ/min	60 5	37 0	126 6	112 0	24 2	21 7
M B 1 6 /min	43 2	44 1	96 3	107 0	43 5	40 0
F B 1 7 /min	54 9	59 2	133 0	161 2	40 8	36 3
L H 1 3 γ/min	50 1	44 1	85 7	101 0	57 4	41 1
S N 4 0 γ/min	96 7	91 1	288 0	353 4	23 6	15 7
J S 1 2 γ/min	91 0	85 5	159 5	163 3	57 8	52 5
H J 1 4 γ/min	72 1	100 5	241 4	359 1	29 8	27 6
Mean	74 4	75 7	197 1	230 6	41 2	34 9
	30 5	28 7	148 1	159 6	13 7	12 0
t	0 445		3 34		3 76	
p	> 60		< 01		< 01	

GFR Glomerular filtration rate (C) = C × 100 / 100 C.. % pl m per tes FF Filtration fraction = GFR / ERPF

ERPF Effective renal plasma flow = C × 1 / 0 9

trated in Fig 1 A comparison of the in crease in cardiac output and renal blood flow demonstrated a proportionately greater rise in cardiac output in 9 of the 12 subjects Renal blood flow increased in proportion to cardiac output in 2 sub jects (B K and M B) and more than cardiac output in one subject (E B) Mean peripheral venous pressure fell sig nificantly in all subjects whereas mean systemic arterial pressure showed slight and inconsistent changes Systemic vascu lar resistance (SVR) and renal vascular resistance (RVR) invariably decreased SVR decreased proportionately more than RVR for all subjects except B K and E B This is illustrated in Fig 2 which demon strates the relationship of SVR to RVR before and during infusion and in Table I by the ratio RVR/SVR Although ERPF increased to or toward normal in all sub jects the effects on glomerular filtration rate (GFR) were slight and variable as is illustrated in Fig 3 Five subjects had increased GFR as well as ERPF however in only one subject (R C) did the GFR

Urine flow (/min /M)		Na excretion (mEq /min /1 73 M)		Serum N (mEq /)		C /C (⁻)	
Mean control	Mea isoprot	Mean control	Mean isoprot	Mea ontrol	Mean isoprot	Mea control	Mean isoprot
1 05	1 08	0 2 4	0 349	0 126	0 130	2 84	3 6
0 63	1 14	0 005	0 01	0 134	0 131	0 10	0 29
0 46	0 52	0 010	0 012	0 130	0 133	0 09	0 11
1 46	2 47	0 099	0 118	0 137	0 138	0 80	0 98
2 30	1 72	0 079	0 071	0 129	0 127	0 15	0 12
0 63	1 69	0 127	0 170	0 129	0 133	1 47	2 25
0 30	0 36	0 023	0 028	0 142	0 138	0 37	0 46
0 48	0 47	0 105	0 142	0 138	0 135	1 38	1 78
0 58	0 53	—	—	—	—	—	—
3 07	2 94	—	—	—	—	—	—
2 00	5 04	—	—	—	—	—	—
0 90	2 78	—	—	—	—	—	—
1 15	1 73	0 078	0 107	0 133	0 133	0 90	1 20
0 86	1 39	0 076	0 116	—	—	0 75	02 1
1 97		1 93		—		3 00	
> 05		> 20		—		< 02	

C/C 100 = ⁻ fl d Na creted C flod m cl ranc = Sta d d devi d

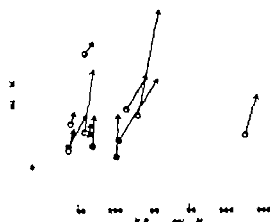


Fig. 1. See text.

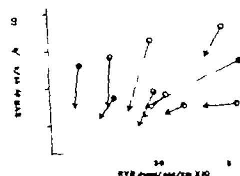


Fig. 2. See text.

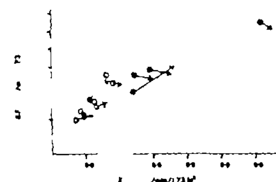


Fig. 3. See text.

increase to the extent of the ERPF. Accordingly, the FF decreased to normal in 3 subjects and toward normal in the other subjects.

The effects on the flow of urine were variable. 9 subjects showed a comparative increase and 3 subjects a decrease in flow. However, the changes in the flow of urine for the group were not statistically significant. Figs. 4 and 5, which relate urine flow (UF) to ERPF and GFR, demonstrate that 4 subjects (J.S., N.K., J.M., E.D.) had increases in the flow of urine with increases in ERPF despite relative decreases in GFR.

Concentrations of sodium in the urine were determined before and during infusion of the drug for 8 of the 12 subjects. Figs. 6 and 7 illustrate the relationships of sodium excretion to GFR and ERPF. Four subjects (R.C., B.K., M.B., E.B.) had increases in the excretion of sodium with associated increases in ERPF and GFR. Three other subjects (N.K., E.D., J.M.) had increased excretion of sodium despite a decrease in GFR. Sodium excretion fell in one subject (F.G.). The effects on the excretion of sodium were not statistically significant, as is shown in Table II. However, when the amounts of filtered sodium per minute were compared to that excreted per minute (C_{Na}/C_I), a significant increase in the percentage of the filtered sodium which was excreted was noted for the group as a whole, as is also shown in Table II.

Discussion

In these studies, isoproterenol increased cardiac output and ERPF for all subjects with congestive heart failure regardless of the type of heart disease, rhythm present (heart block excluded), or state of digitalization. The increased cardiac output was invariably associated with a decrease in systemic and renal vascular resistances. These findings are in contrast to the effects of most other sympathomimetic amines on systemic and renal vascular resistances.[15, 31, 33]

Although RVR was noted to decrease, a comparison of RVR and SVR (expressed as RVR/SVR in Table I) before and during infusion of isoproterenol demonstrated a greater lowering of systemic than of renal vascular resistance in 10 of the 12 subjects studied. The vascular beds which participated in this lowering of systemic vascular resistance were not identified in this study. However, Ahlquist,[4] in studying the effects of isoproterenol in experimental animals, found a slightly greater decrease in vascular resistance in the mesenteric and femoral vascular beds than in the renal vascular bed.

Although ERPF increased and FF de-

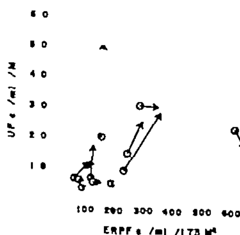


Fig 4 See text

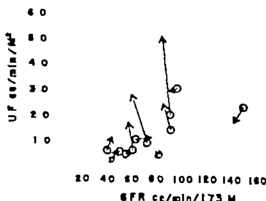


Fig 5 See text

creased to or toward normal in all subjects the effects of isoproterenol on the flow of urine were variable and show no statistically significant change This may be related to the GFR values which changed little However in the subjects who did show a definite increase or decrease in the flow of urine this change in the flow of urine was not related to the magnitude or direction of change in GFR Aviado[22] using direct intra arterial injections of isoproterenol observed increases in RBF and a decreased flow of urine which he postulated might be due to a relaxant effect of this drug on the smooth muscle of the renal pelvis and ureters The mechanisms which accounted for a rise in the rate of urine flow in some subjects and a fall or no change in others were not demonstrated in this study

The increased excretion of sodium that was observed for 7 of 8 subjects is of interest Figs 6 and 7 illustrate that this increased excretion was not related either to an increased GFR or ERPF Furthermore changes in the excretion of sodium seemed to be unrelated to changes in the flow of urine The changes in the excretion of sodium may be related to the increased cardiac output and/or shifts of blood distribution leading to alterations in the hormonal mechanisms concerned with retention of sodium in congestive heart failure

It has been previously noted that the effects of isoproterenol on cardiac output heart rate systemic vascular resistance oxygen consumption arterial venous oxygen difference and venous pressure are similar to the effects of theophylline in both normal subjects and subjects with congestive heart failure[17,18] Changes in renal function that were observed during infusion of isoproterenol in this study were also compared with changes in renal function during infusion of theophylline in subjects with congestive heart failure as reported by others[19,23] The effects of

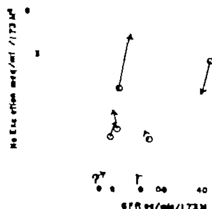


Fig 6 See text



Fig 7 See text

these two drugs on C I R are similar The proportionate rise in RBF and fall in I I observed with isoproterenol are greater than those reported with theophylline However the increase in the flow of urine and the excretion of sodium that was reported with theophylline is greater than that observed during administration of isoproterenol in this study

Summary

The cardiovascular renal effects of isoproterenol were studied in 12 male subjects with congestive heart failure due to heart disease of varied etiologies Unlike the majority of sympathomimetic amines isoproterenol increases renal and systemic blood flow and reduces renal and peripheral vascular resistance Although effective renal plasma flow was increased in all subjects no significant change in glomerular filtration rate or consistent change in the flow of urine was observed during infusion of isoproterenol The excretion of filtered sodium during infusion of the drug increased in 7 of 8 subjects

The authors ... acknowledge the ... t h al ... t ... of I urn St hurd J Thompson ... C net I n and Con ... Thom

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these two drugs on C I R are similar The proportionate rise in RBF and fall in I F observed with isoproterenol are greater than those report d with theophylline However the increase in the flow of urine and the excretion of sodium that was re ported with theophylline is greater than th t bserved during administration of iso proterenol in this study

Summary

The cardiovascular renal effects of iso proterenol were studied in 12 male subjects with congestive heart failure due to heart disease of varied etiologies Unlike the majority of sympathomimetic amines iso prot renol increases renal and systemic blood flow and reduces renal and peripheral vascular resistance Although effective renal plasma flow increased in all subjects no significant change in glomerular filtration rate or consistent change in the flow of urine was observed during infusion of isoproterenol The excretion of filtered sodium during infusion of the dru in creased in 7 of 8 subjects

The h rs w h t acknowledge the aluable techni l tance of I ra Steinhardt Joan Th mps Genett F in and Conn Th ma

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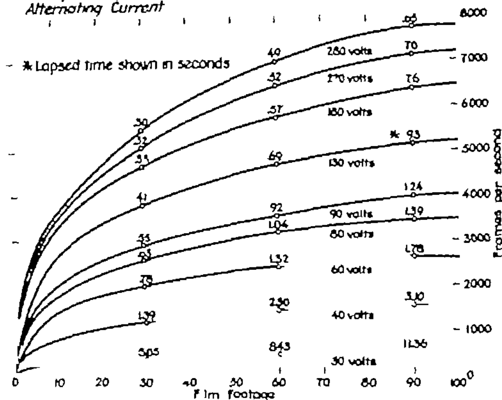


Fig 1 The chart indicates the film frame rate and footage time lapse at increasing AC voltage inputs Film speeds up to 5 000 frames per second are obtainable with variable AC transformer but an additional Goose Control Unit is required for the higher speeds

munication is to describe a system which surmounts these difficulties and to outline briefly how this system has been applied in certain aspects of circulatory function

Method

The camera is a Wollensak WF17 16 mm Fastax utilizing a rotating prism shutter capable of film speeds up to 8 000 pictures per second Its unique feature is a double lens system which permits the combined recording of motion picture and oscillographic data Therefore any electrical (ECG) mechanical (pressure) or sonic (phonocardiogram) event may be superimposed on the motion picture frames Fifty millimeter f/2.0 Raptar lenses are employed in both motion picture and oscillographic systems but 63 mm 75 mm or longer focal length lenses may be used when additional field detail is desirable

Wollensak Optical Co Rochester N Y

The camera is furnished with two 115 volt AC DC motors one to drive and the other to take up the 100 foot roll of film In the lower speed ranges power for 350 to 1 500 pictures per second is provided by a 0 30 volt DC rectifier which is controlled by a variable AC transformer In the intermediate ranges up to 5 000 pictures per second a variable AC transformer 0 135 volts is employed For maximum film speeds a Goose Control Unit is required This unit incorporates an AC autotransformer with a maximal output of 280 volts The unit allows for synchronization of the camera with the event under study and provides a time delay mechanism which regulates sprocket starting torque in order to avoid damage to the film perforations when the voltages required for the highest film speeds are applied Time lapse and speed characteristics at various AC inputs are shown in Fig 1 The precise film speed at



Fig. [illegible] Photograph of camera to show oscilloscope to be mounted [illegible] top camera body just above the oscillographic lens which is set [illegible] the door of the film magazine. The metal assembly which holds two plane mirrors mounted opposite each other at 45 degree angle [illegible] retracted. The high intensity Xenon lamp stands opposite the camera.

moment is provided by a timing light which makes 120 pips or marks per second between sprocket holes when energized by a 60 cycle current. The light can also inscribe 100 or 1,000 pips per second when activated by a timing light generator.

The oscillographic lens is mounted on the camera door at right angles to the motion picture lens. Laboratory and operating room conditions require that the oscilloscope face and its lens be aligned and in proper focus for any camera eleva

tion and tilt angle This has been accomplished in the following manner The cathode ray tube of a Tektronix dual beam oscilloscope Type 502* was removed and mounted separately in a metal housing atop the camera body The face of the cathode ray tube is situated just above and in the same plane as the camera door (Fig 2) The circuitry and controls of the oscilloscope are mounted on a metal shelf at the base of the camera tripod and for simplicity the power supplies of the tube and camera are combined in a single cable which runs from the face of the oscilloscope control panel to the undersurface of the housing of the cathode ray tube Two plane mirrors which are set at angles of 45 degrees in the same vertical plane reflect the cathode tube image into the oscilloscope lens through an angle of 180

*Tektronix, Inc, Portland Ore



Fig 3 The metal assembly po tio for recording od the cilloscope beam are reflected through an angle of 180 degrees into the oscillographic lens The tw mirrors are oppos te each other t the bend of the C haped hou ng

Table I. Illumination characteristics of Xenon quartz lamp; lamp to subject distance of 3 feet

Lamp output (kilowatt)	Filter	Full shot	
		Area covered	Foot candles
2.5	Clear	3 inch diameter	120 000
5.0	Clear	3 inch diameter	240 000
7.5	Clear	3 inch diameter	480 000
2.5	Medium	7 inch diameter	35 000
5.0	Medium	7 inch diameter	70 000
7.5	Medium	7 inch diameter	140 000
2.5	Maximum density	10 inch diameter	15 000
5.0	Maximum density	10 inch diameter	30 000
7.5	Maximum density	10 inch diameter	60 000

degrees. The mirrors are set at the right angle joints of a tubular metal assembly which has the shape of a reversed "C." The inner surfaces of the metal are blackened to absorb stray light. This metal assembly is hinged to the front of the housing of the cathode-ray tube and is readily swung in and out of position. Fig. 3 shows the entire assembly in position for recording.

The Tektronix dual beam oscilloscope is ideally suited for photographic purposes. Its sensitivity, permitting gains up to 200 microvolts per centimeter, makes it unnecessary to employ additional preamplifiers for electrocardiography and phonocardiography, thus simplifying the instrumentation. It is fitted with a P 11 blue phosphor of short persistence and high intensity, adequate for the purposes of high-speed cinematography. During recording the horizontal time sweep of both beams is suspended. The phosphorescent dots move only vertically, and the film movement acts as the horizontal time base.

Illumination is provided by a single high-intensity WI 360 Xenon lamp.* The lamp bulb is quartz. The source size is approximately 5 mm. in diameter and has a color temperature of 5,700°K. The illumination characteristics of the lamp are shown in Table I. The control unit is cased in a portable console. The voltage striking circuit makes use of a 25 kilovolt repeating pulse at a current flow of 25 amperes. The lamp simmers at 700 watts, and one of three power levels may be selected, each with its own period limiting circuit. At 2.5 kilowatts the pulse is of 10 second duration, at 5.0 kilowatts it is of 5 second duration, and at 7.5 kilowatts the duration is 2 seconds. Power for the unit is furnished by a 42 volt supply from seven 6 volt wet batteries. Silicon rectifiers may also be used as the power supply. The output of heat is low, so that no discomfort is felt on the face if the lamp is brought to a maximum spot at a distance of 3 feet and pulsed at 7.5 kilowatts. This provides an illumination of 140,000 foot candles with a medium filter, and 480,000 foot candles with a clear filter.

The color temperature of 5,700°K makes possible the use of daylight film. For color photography, both Superanscochrome and commercial Ektachrome ER perforated for high-speed photography have been very satisfactory. The latter film is currently preferred because it is less grainy.

Motion picture analysis is facilitated by a projector† which allows the choice of viewing at 16 pictures per second, 2 pictures per second, frame by frame advance, or still projection. It also incorporates a frame counter. In this manner the film speed at any time can be determined from the timing light pips, and the oscillographic and motion picture events may be temporally correlated. It has also been useful in still presentation of motion picture

*Wollensak Optical Co., Rochester, N. Y.

†Wollensak Optical Co., Rochester, N. Y.

data to trace silhouettes from representative projected frames during different parts of the cardiac cycle and to superimpose them in a composite drawing

Discussion

The present system of high speed cinematography incorporates a number of recent advances in instrumentation and technique and has particular application to the study of cardiovascular phenomena In addition to the unique motion picture and oscillographic dual lens systems improved prism shutter design and view finder units have enhanced resolution and over all film quality at high frame rates The availability of a high intensity cool quartz lamp has greatly simplified lighting problems Illumination is provided by a single lamp replacing the banks of 12 or more photospot lights which were previously required Drying or burning of tissues is not noted at full spot when a medium filter is used or at flood when the filter is clear

The addition of an oscillographic lens permits the combined recording of cardiovascular motion sounds pressures and the electrocardiogram This has expanded the scope of cinematography as a method for analyzing circulatory events and it has been useful both in animal research and in clinical investigation

We have used the technique in the surgical laboratory to study the sequence of right ventricular contraction the effects of ventriculotomy on the contraction of the right ventricle and the behavior of outflow tract patches In these studies to be fully reported elsewhere high speed cinematography with simultaneous electrocardiography and phonocardiography was useful in establishing the asynchronous character of right ventricular contraction and in analyzing the adverse effects of vertical ventriculotomy on the pattern of right ventricular motion

The method is also suitable for the study of externally recordable circulatory events such as cardiac impacts on the chest wall and arterial and venous pulsations For example in a case of carcinoid syndrome with tricuspid insufficiency motion analysis disclosed the bifid character of the systolic jugular pulsations A second peak appeared 10 milliseconds after the initial impact and 27 milliseconds after the Q wave of the electrocardiogram suggesting a venous bisferiens phenomenon

In conclusion the method is particularly suitable for the analysis of complex intrinsic movements of the heart and great vessel as viewed from the surface of the heart However photography of the heart does require extensive thoracotomy and pericardial resection which limits the validity of observations in regard to rotational movements and since the distance from the heart to the lens may not remain constant throughout the cardiac cycle apparent changes in heart volume cannot be directly interpreted

Finally it is important to select a camera speed appropriate to the event under study since excessive film speeds may obscure slow displacements just as the details of rapid motion are lost at frame rates which are too slow Thus the jugular bisferiens pulse in tricuspid insufficiency was well recorded at 240 pictures per second whereas the details of motion in the outflow tract of the right ventricle were best studied at 800 to 1 200 pictures per second

Summary

1 A method of high speed cinematography for the study of cardiovascular motion has been described

2 Its unique feature is a dual lens system which enables the simultaneous recording of motion picture and oscillographic frames This innovation allows for the appearance of electrocardiogram sounds and pressures on the particular aspect of cardiovascular motion under study and makes possible the use of the camera for the precise measurement of circulatory events

3 The present method also incorporates recent improvements in high speed shutter systems focusing devices frame speed timers and light sources In particular the utilization of a high intensity light source with low output of heat has avoided tissue damage and increased the applicability of the unit

4 The application of the method both to the experimental laboratory and to clinical research is briefly described

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Acute effects of intravenous chlorothiazide upon cardiovascular hemodynamics

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The mechanisms of action of chlorothiazide in reducing blood pressure have not been definitively established. Various possibilities have been proposed. These include (1) decrease in total circulating plasma volume secondary to the diuretic effects of this agent, resulting in diminished cardiac filling and thereby in reduced cardiac output; (2) changes in extracellular and intracellular electrolyte relationships resulting in decreased arteriolar tone or dehydration of "waterlogged" arterioles, hemodynamically reflected as diminished total peripheral resistance; (3) vasodilation by direct effect upon peripheral vessels or upon the central nervous system; (4) decreased responsiveness to endogenous vasopressor mechanisms. The present study, which concerns the acute effects of the intravenous administration of chlorothiazide upon cardiovascular dynamics in hypertensive and normotensive subjects, was performed in order to gain more information about the mechanisms of action of this drug.

An important property of chlorothiazide is a limitation of the hypotensive effect to the hypertensive state. Therefore, it appeared that an investigation of this type could also serve to study the properties of the circulatory system in patients with hypertension, especially as it differs from the normal state.

Method

Twelve patients, 5 women and 7 men, were the subjects of this study (Tables I and II). They ranged in age from 32 to 65 years. Ten patients (Patients 1-10) had persistent systemic arterial hypertension as defined by systolic pressures greater than 140 mm. Hg and diastolic pressures greater than 90 mm. Hg (except Patient 6, in whom the control pressures averaged 187/75 mm. Hg). Two patients (Patients 11, 12) were normotensive. Specific antihypertensive drugs and diuretics were avoided for several weeks prior to the study. Further information concerning associated diseases, the presence of heart failure, and ancillary cardiac therapy are tabulated in Table I.

The patients were hospitalized for at least 1 to 2 weeks. During this period routine clinical observations were made and pertinent laboratory data obtained. Fluid balances were evaluated according to daily fasting weights, daily outputs of urine, and frequent determinations of serum electrolytes and, in some patients, of urine electrolytes.

The acute effects of intravenous chloro-

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thiazide upon cardiovascular hemodynamics were then studied. The patients were in the resting recumbent positions and were not given premedication. The standard technique for right heart catheterization was performed in 10 cases (Patients 1, 4-12). In one case (Patient 2) systemic arterial pressures (direct), cardiac outputs (indicator dilution method), and heart rates were measured directly. In Patient 3 only systemic arterial pressures (direct) and heart rates were measured. Control data were obtained initially. Cardiac outputs were measured by the indicator dilution method according to Hamilton and co-workers.* Known amounts of dye (Cardio-green†) were injected rapidly into the pulmonary artery (Patients 1, 4-7, 9-12) or right atrium (Patient 8) through the catheter or into an antecubital vein (Patient 2) through an indwelling arterial needle (Cournand) and time concentration curves of dye were obtained from the peripheral (brachial) artery by means of a cuvette densitometer in conjunction with a constant flow system. The volume of blood between the point of injection and the site of sampling (including all temporally related sites) was calculated as the product of cardiac output and mean circulation time (central blood volume). Pressures were obtained with Statham strain gauge transducers and recorded on a multichannel oscillographic photographic recorder. Mean pressures were obtained by electrical integration of the pressure pulses. The point of zero reference for measurements of intracardiac pressures was taken at 5 cm. below the angle of Louis. Total pulmonary vascular, pulmonary arteriolar, and total peripheral resistances were calculated according to standard formulas (Poiseuille). Resistance is expressed in dynes per second per cm.$^{-5}$ by the use of conversion factors.‡

Since the parameters measured did not vary significantly during control periods, only average values are tabulated (Tables I and II).

After the control data were obtained, chlorothiazide, 0.75 to 1.00 Gm. in isotonic solution, was administered intravenously over a period of 5 to 10 minutes. Measurements were then made during the following 140 to 175 minutes. This latter period will henceforth be referred to as the *immediate postdrug phase*. Pressures and heart rates were measured frequently. Cardiac outputs were determined 3 to 6 times by the indicator dilution method beginning 5 to 25 minutes (average 16 minutes) to 70 to 170 minutes (average 138 minutes) after administration of the drug. Vascular resistances, stroke volumes, and central blood volumes were calculated from these data.

The following were measured frequently during the control periods and during the immediate postdrug phases: peripheral arterial hematocrits (Patients 1, 3, 5-12) and outputs of urine and intakes of fluid (Patients 1, 3, 4, 6, 8-12) (subjects undergoing cardiac catheterization received a constant infusion of 5 per cent glucose). The following were measured at least once during the control periods and at approximately 100 to 150 minutes after administration of the drug: total plasma volume (I^{131} labeled human serum albumin method) converted to total blood volume by the use of peripheral hematocrits (volumes during the second periods were measured 10 to 15 minutes after the administration of additional radioactive material) (Patients 1, 8, 10); ventilations, oxygen consumptions, and respiratory quotients (analysis of expired air collected in a Tissot spirometer during 3 minutes of quiet breathing) (Patients 2-12); and systemic arterial oxygen saturations[§] (Patients 5, 7, 8, 10-12).

Changes in cardiovascular hemodynamics were evaluated in terms of statistical probabilities. In order to determine whether changes are due to chance variations per se or to the action of an introduced variable (chlorothiazide in this study), 29 consecutive right heart catheterizations performed in this laboratory in adults with varied types of heart disease were analyzed. In each of these studies at least two control resting cardiac outputs (indicator dilution method) and multiple pressures were measured and resistances calculated at intervals of 22 to 113 minut

[illegible]

[illegible]

(average 41 minutes) while the patients states were considered to be constant. Mean values standard deviations and 95 per cent confidence limits for the various measures of cardiovascular dynamics were established in order to define the statistical ranges for chance variations between two or more measurements. A wide range of abnormalities in cardiodynamics was present in this control group as would be expected in any series of patients with heart disease. It was thought therefore that greater reliability in an evaluation of significance would exist if the confidence limits were expressed in terms of percentage differences rather than differences in absolute values. Two exceptions are pulmonary wedge and right ventricular end-diastolic pressures. These parameters are expressed in terms of absolute changes because (1) only minimal variations usually occur during a resting state and (2) small variations in their usually low numerical values frequently result in inordinately high percentage changes.

Changes in cardiovascular dynamics in the present series of 12 patients who received chlorothiazide are evaluated in terms of statistical *significance* at the 5 per cent level based upon the confidence limits as determined from the control group (*vide supra*). Changes which are considered to be statistically significant are appropriately indicated in Tables I and II and in the description of the *results*. *In the* latter section maximal percentile changes in the various parameters are indicated in parentheses whereas broader statements are made concerning durations of over all significant changes. The patients are divided into two groups: those in whom chlorothiazide induced systemic arterial hypotension during the immediate post drug phases (Group A) and those in whom the systemic blood pressures did not change during these periods (*Group B*).

Results

Group A. Subjects in whom chlorothiazide induced systemic arterial hypotension during the immediate postdrug phases (Patients 1 7) (*Tables I and II*). In patients (Nos 1 7) significant declines in systolic (average −33 per cent) diastolic (average −31 per cent) and mean (average −34 per cent) systemic arterial pressures occurred during the immediate postdrug phases. These 7 patients had pre-existing hypertension. In 3 subjects (Nos 2 6) hypotension occurred 20 66 and 50 minutes respectively after chlorothiazide had been administered and lasted an average of 29 minutes. In the other 4 subjects (Nos 1 3 5) hypotension appeared 26 to 110 minutes (average 62 minutes) after the drug was administered and persisted throughout the remainder of the immediate postdrug phases. In 4 (Nos 1 4 6) of these 7 subjects significant decreases in cardiac outputs (average −34 per cent) occurred concomitant with the declines in blood pressures. The decreases in cardiac outputs were associated with significant reductions in stroke volumes (average −31 *per cent*) and in central blood volumes (average −26 per cent).

Total peripheral resistances declined significantly (average −30 per cent) in 3 subjects (Nos 1 2) and increased significantly (average +25 per cent) in 3 others (Nos 4-6) concomitant with the reductions in systemic arterial pressures. It is of interest that in the latter 3 patients the extent of declines in cardiac outputs were greater (−34 to −47 per cent) than in the former 3 patients (−19 −27 and +15 per cent). This will be commented upon later.

In Patient 1 control pressures in the lesser circulation were normal and did not change after chlorothiazide had been administered. In 4 subjects (Nos 4 7) moderate degrees of pulmonary hypertension were present in the control periods. In these patients pulmonary arterial pressures decreased to or almost to normal during the immediate postdrug phases. In 3 patients (Nos 4-6) control right ventricular end-diastolic pressures were moderately elevated. In 2 patients (Nos 4 6) significant declines occurred during the immediate postdrug phases. Control pulmonary wedge pressures were elevated in 2 patients (Nos 5 6) in whom they were measured. Significant reductions were noted in both patients after the drug was administered. There were no changes in pulmonary arteriolar resistances.

There were no significant changes in the following parameters in those subjects in

Table I Cardiovascular hemodynamics before and after administration of chlorothiazide

Patient number sex age	Clinical status		Pressure (mm Hg) Peripheral artery S	D	M	T	Pulmonary artery S	D	M	T
1 F 32	Diabet chronic nephritis mild azotemia Therapy salt intake unlimited udm	I	180	111	140		21	9	14	
		II	107	76	86	76	25	10	16	
		Diff	−41	−32	−39	(45 140E)	+16	+10	+12	
M 35	Therapy salt intake limited	I	184	110	143					
		II	91	48	63	35				
		Diff	−51	−56	−56	(20 35)				
3 F 43	Therapy salt intake limited	I	162	91	114					
		II	96	60	79	95				
		Diff	−41	−34	−31	(26 175I)				
4 M 61	LHD RHD Therapy digoxin salt intake 1 0-1 5 Gm dail	I	254	110	155		50	18	29	
		II	204	86	123	150	24	8	13	175
		Diff	−20	−22	−21	(110 175E)	−52	−56	−55	(25 130F)
5 F 49	MS LHD RHD Therapy digoxin salt intake 4 0-5 0 Gm dail	I	187	107	130		41	22	29	
		II	154	87	118	170	28	14	20	130
		Diff	−18	−15	−9	(63 170F)	−32	−36	−31	(25 130F)
6 F 65	Coronary artery disease LHD RHD Therapy digoxin salt intake 1 0-1 5 Gm daily	I	187	75	107		43	17	24	
		II	157	63	91	115	33	15	21	170
		Diff	−16	−16	−15	(76 115)	−23	−12	−13	(110 170F)
7 M 48	LHD Therapy salt intake 4 0-5 0 Gm daily	I	187	132	156		43	21	25	
		II	111	81	92	50	18	6	12	66
		Diff	−41	−39	−41	(50 73)	−58	−71	−52	(25 145F)
8 M 48	Therapy salt intake unlimited	I	217	12	154					
		II	212	119	146					
		Diff	−2	−6	−5					
9 M 41	MI MS LHD RHD Therapy digoxin salt intake 1 0-1 5 Gm daily	I	143	100	113		67	40	50	
		II	135	87	108		58	36	45	
		Diff	−6	−13	−4		−13	−10	−10	
10 F 6	Chronic nephritis LHD RHD Therapy digitalis salt intake 4 0-5 0 Gm daily	I	231	107	158		73	27	44	
		II	221	101	147		64	24	41	
		Diff	−4	−4	−7		−12	−11	−7	
11 M 51	LHD Therapy salt intake limited	I	123	66	85		31	10	17	
		II	116	64	76		25	9	14	
		Diff	−6	−3	−11		−19	−10	−18	
12 M 3	MI MS AS LHD RHD Therapy digitalis salt intake 1 0-1 5 Gm daily	I	121	4	94		105	46	62	
		II	112	68	86		94	42	59	
		Diff	−7	−8	−9		−10	−9	−5	

For footnotes see T bl II

Pulmonary wedge		Right ventricular		Resistance (dynes sec cm)					
				Total systemic		Total pulmonary vascular		Pulmonary arteriolar	
D	T	D	T		T		T		T
6		6 5 −1		2 300 1 760 −23	35 (15 5F)	60 200 −23		100	
				2 750 2 700 −20	20 (20)				
		6 0 −6	170 (60 170F)	2 930 3 480 +16	1 0 (170E)	630 370 −41		200	
22 14 −8	58 65	6 4 −2		2 450 3 400 +28	120 (25 120E)	520 720 +28		195 2 0 +28	
12 9 −3	90 170	10 7 −3	120 (120 170F)	3 000 4 400 +32	110 (25 150E)	720 950 +24		470 410 −13	
		4 3 −1		5 000 2 700 −46	60 (60 73)	730 310 −58	60 (60 3)		
		1† 0 −1		2 160 2 490 +13					
29 23 −6	60 120	18 15 −3	60 (60 65)	3 660 2 560 −30	103 (25 150F)	1 770 1 100 −38	1 0 (160 1 0F)	660 525 −21	
		6 4 −2		3 300 2 800 −15					
2 3 +1		3 0 −3	45 (45 97E)	2 540 2 040 −19		440 360 −18		320 360 +11	
34 32 −		6 4 −		2 030 2 300 +12		1 310 1 650 +20		700 770 +9	

Table II. Cardiovascular hemodynamics and outputs of urine before and after administration of

Patient		O[illegible] consumption (ml./min./M.²)	T	Cardiac index (L./min./M.²)	T	Heart rate (beats/min.)	T	Stroke volume (c.c./beat)	T
1	I	101		2 99		103		49	
	II			2 43	75 (75I)	92		40	75 (75Γ)
	Diff			−19		−11		−18	
2	I	136		2 10		78		52	
	II	137		1 54	140 (140I)	73		40	140 (140Γ)
	Diff	+1		−2		−6		−23	
3	I	91				75			
	II	71	120			60	35 (35 170I)		
	Diff	−24				−20			
4	I	118		2 40		5		73	
	II	138	100	1 59	1 0 (140 170Γ)	61		51	170 (140 170Γ)
	Diff	+14		−31		+11		−30	
5	I	181		2 40		95		44	
	II	176		1 27	130 (65 130I)	105		27	130 (30 130I)
	Diff	−3		−47		+10		−50	
6	I	114		1 69		78		37	
	II	109		1 09	110 (50 110)	73		25	110 (50 110)
	Diff	−4		−35		−6		−32	
7	I	142		1 15		100		1	
	II	123		1 35		85	80 (80)	31	80 (80)
	Diff	−13		+15		−15		+23	
8	I	117		2 6		87		65	
	II	1 1		2 30		100		55	
	Diff	+6		−1		+13		−15	
9	I	178		1 25		112		21	
	II	169		1 77	15 (45 150I)	103		33	105 (25 150I)
	Diff	−5		+79		−8		+36	
10	I	117		2 58		105		38	
	II	113		2 26		97		34	
	Diff	−4		−12		−8		−11	
11	I	1 5		1 32		60		46	
	II	137		1 83		65		50	
	Diff	+9		+16		+8		+8	
1	I	157		2 1		110		33	
	II	147		1 94		121	105 (105 135Γ)	23	125 (125)
	Diff	−10		−17		+13		−24	

Footnotes for Tables I and II
Diff [illegible] between I and II are given as absolute values.
†Right [illegible] mean pressure.
§ Systolic D Diast [illegible] [illegible] acute study [illegible] Left [illegible] Right [illegible] Cardiac hemodynamics during the immediate post [illegible] phases. Values [illegible] maxima. By diff [illegible] from the [illegible] locate the times after drug adm [illegible] were measured. [illegible] I and II were present [illegible] numbers with [illegible] maximum. The appropriate space is left blank if no significant changes occurred. Outputs of urine [illegible] indicate total amount [illegible]

chlorothia_ide

Central blood volume ( )	Central blood volume T	Hematocrit (%)	Hematocrit T	Systemic artery O_2 saturation (%)	Systemic artery O_2 saturation T	TPV ( )	TBV (cc)	Urine output (c)
1 075 870 −24	75 (75E)	26 26 0		96		2 210 2 260 +2	3 100 3 060 −1	50 120
1 450 1 100 −24	140 (140E)							
		30 31 +3						40 500
1 400 1 070 −24	170 (140-170E)			93				750 750
1 200 810 −3?	130 (130E)	40 40 0		94 91 −3				
860 630 −27	50 (50-110)	42 40 44 −5 +5				4 370	7 800	150 560
1 640 1 660 +1		43 47 −2		89 93 +4				
940 8 0 −7		40 39 −3		94 96 +2		2 820 2 940 +4	4 00 4 800 +2	50 500
1 430 1 900 +25	105 (25 150E)	51 52 +2		95				50 475
1 400 1 240 −11		42 42 0		83 83 0		2 430 2 420 0	4 200 4 200 0	70 200
1 75 1 600 +20		42 43 +2		94 95 +1		3 150	5 420	70 140
1 790 1 4 0 −18		30 31 +3		91 90 −1		3 670	5 260	100 265

decompensation. MS Mitral st osis. MI Mitral insufficiency AS Aortic ste osis. I Cardiovascular hemodynamics during co tr l of th trol period w b tated Diff d t ns per c differences between I and II In column T numbers outside parentheses I durat times d ring which over-all significa changes were present. Th latter incl des changes which are significant but less than period TPV T tal plasm ol me TBV Tot l blood vol m

whom they were measured in the control periods and during the immediate postdrug phases: systemic arterial hematocrits, systemic arterial oxygen saturations, respiratory quotients, ventilations, oxygen consumptions, and total plasma and total blood volumes.

Outputs of urine and intakes of fluid were measured in 4 subjects (Nos. 1, 3, 4, 6) during the control and immediate postdrug phases. Three of these patients (Nos. 1, 4, 6) received 450 to 500 c.c. of isotonic glucose intravenously at a constant rate during the entire study. In Patients 1, 3, and 6, outputs of urine increased by 70 to 450 c.c. (average 307 c.c.) during the immediate postdrug phases as compared to control periods, and in Patient 4 no increase in the output of urine occurred. In Patients 3, 4, and 6 the total outputs of urine exceeded the intakes of fluid by 200 to 950 (average 567 c.c.), whereas in Patient 1 the intake of fluid exceeded the output of urine by 330 c.c. In Patients 3, 6, and 7, concentrations of sodium, chloride, and potassium in the urine increased twofold in the immediate postdrug phases as compared to control periods.

Group B. Subjects in whom no changes in systemic arterial pressures occurred during the immediate postdrug phases (Patients 8-12) (Tables I and II). In 5 subjects (Nos. 8-12) no changes in systemic arterial blood pressures occurred during the immediate postdrug phases. Three of these patients (Nos. 8-10) had pre-existing hypertension and 2 (Nos. 11, 12) were normotensive. In one case (Patient 9) significant increases in cardiac outputs and reductions in total peripheral resistances occurred from 45 to 150 (the last determination) minutes after the drug was administered. Stroke volumes and central blood volumes were increased at the same time.

In 3 patients (Nos. 9-12) pulmonary arterial pressures were elevated to varying degrees during the control periods. No changes occurred after chlorothiazide had been given. In Patients 9 and 12 control pulmonary wedge and right ventricular end-diastolic pressures were considerably elevated. In Patient 9 significant reductions occurred in these pressures after the drug had been given, whereas there were no changes in Patient 12. In Patients 10 and 11, control right ventricular end-diastolic pressures were normal. In Patient 10 no changes were noted during the drug period, whereas a slight decrease occurred in Patient 11.

There were no changes in pulmonary arteriolar resistances.

There were no significant changes in the following parameters in those subjects in whom they were measured in the control periods and during the immediate postdrug phases: systemic arterial hematocrits, systemic arterial oxygen saturations, respiratory quotients, oxygen consumptions, ventilations, and total plasma and total blood volumes.

Outputs of urine and intakes of fluid were measured during the control and immediate postdrug phases. The patients received 450 to 500 c.c. of isotonic glucose intravenously at a constant rate during the entire study. The outputs of urine increased by 40 to 400 c.c. (average 196 c.c.) during the immediate postdrug phases as compared to control periods. In Patients 8 and 9 total outputs of urine exceeded intake of fluid by 75 to 100 c.c., whereas in Patients 10, 11, and 12 the intakes of fluid exceeded the outputs of urine by 135 to 260 c.c. In Patient 9, concentrations of sodium and chloride in the urine increased fivefold and the concentration of potassium twofold during the immediate postdrug phases, and in Patient 11 there was a slight increase in the urinary concentration of sodium, a fivefold increase in the concentration of potassium, and a twofold increase in the concentration of chloride.

Discussion

Conflicting interpretations have been offered to explain the mechanisms by which chlorothiazide exerts its antihypertensive action. Probably the most important single question has been whether this drug reduces blood pressure by producing oligemia or by a direct vasodilatory effect or by a combination of these factors.

It has been proposed that the chlorothiazide-induced oligemia is responsible for the reduction in blood pressure.[11] Freis and co-workers[9] call attention to the parallelism between electrolyte and fluid (urine) losses, reductions in extracellular

fluid and plasma volumes and the decreases in blood pressure. In addition the withdrawal of chlorothiazide results in a prompt increase in plasma volume and a rise in blood pressure.[9] Infusions of Dextran have been given to some hypertensive subjects in whom the blood pressure was lowered by chlorothiazide and this resulted in immediate rises in blood pressures and decreases in hematocrits. Dustan and associates[1] and Heider and associates[11] suggest that the primary factor in determining chlorothiazide enhancement of the hypotensive effects of ganglioplegic drugs is the contraction of plasma volume which increases vasomotor tone and hence makes the patient more responsive to the latter drugs.

Observations by others have suggested that the antihypertensive effect of chlorothiazide cannot be explained solely on the basis of oligemia and that there may also be a distinct action of this drug directly or indirectly on blood vessels. Wilkins and co-workers[13,14] have demonstrated that the decline in blood pressure during chlorothiazide therapy may not parallel closely the degree of depletion of electrolytes and water from the body. They have also shown that after prolonged periods of therapy the hypotensive effect may persist without accompanying reductions in body sodium and potassium, extracellular fluid and plasma volume. The simultaneous administration of 9-alpha-fluorohydrocortisone and chlorothiazide to a hypertensive subject resulted in a positive sodium balance, no changes in body weight, but a reduction in blood pressure. A reduction in blood pressure may occur within a few hours after the drug has been administered without significant changes in weight, especially in subjects who had previously had splanchnicectomy.[13,14] In another group of hypertensive subjects, decreases in plasma volumes, blood pressures and cardiac outputs occurred after 7 to 19 days of therapy.[16] Plasma volumes and cardiac outputs rose to control levels after 1 month but blood pressures remained reduced. Crosley and co-workers administered chlorothiazide intravenously to a group of subjects with hypertension. Within 15 to 30 minutes significant decreases in glomerular filtration rate, renal blood flow, and cardiac output occurred. Systemic arterial pressures did not change due to increases in total peripheral resistances. Hematocrits did not change, implying constant plasma volumes.[1]

The results of the present study offer further evidence that chlorothiazide has distinct vasodepressor effects apart from those attributable to oligemia. In those hypertensive subjects in whom chlorothiazide lowered the blood pressure there were no changes in total plasma and blood volumes as indicated by constant hematocrit values and by direct measurements (I[131] labeled human serum albumin). Although the drug induced salt and water diureses in all but one (Patient 4) of the subjects in whom this was measured, there were no consistent relationships between changes in fluid balance and changes in blood pressure. In most subjects in whom hypotension was induced, diureses and negative fluid balances occurred; however, in Patient 1 an increase of only 70 c.c. in the output of urine occurred and the intake of fluid exceeded the total output of urine by 330 c.c. In the hypertensive and normotensive subjects in whom blood pressures did not change during the immediate postdrug phases, diureses were induced by the drug; fluid balances were negative in 2 patients (Nos. 8, 9) and positive in 3 (Nos. 10-12).

The reductions in blood pressures were caused primarily by decreases in cardiac outputs. Reductions in stroke volumes were responsible for the decreases in cardiac outputs. The mechanisms whereby cardiac outputs (or stroke volumes) were reduced are not readily apparent from the data available. Oligemia does not appear to be the major factor for the reasons stated above. Another possibility is a decrease in interstitial fluid pressure (secondary to loss of extracellular fluid) which may reduce vascular tone and thereby cause vasodilation. Since plasma volume may be considered to be in constant equilibrium with interstitial fluid, the absence of changes in plasma volumes in the subjects of the present study would suggest that this factor was not important. Inhibition of myocardial contractility is a possibility but the present data do not permit conclusions in this regard. Another interesting possibility is a redistribution of blood volume from

the central vascular bed to peripheral vessels resulting in a reduction in venous return and thereby in the amount of blood available to the heart. This would imply peripheral vasodilation primarily venous.

In 3 patients (Nos. 1, 2, 7) calculated peripheral resistances decreased, suggesting reductions in arteriolar tone. In 3 others (Nos. 4-6) significant increases in peripheral resistances occurred. The latter however does not necessarily indicate increased arteriolar tones but rather decreases in luminal area or caliber. In general, caliber varies indirectly with the active (smooth muscle dependent) vascular tone and directly with the intravascular force (blood flow or volume) tending to distend the vessel; the result depends on the balance between these two factors.[7] Therefore, a rise in peripheral resistance (or decrease in luminal caliber) may occur in the presence of a decline in vasomotor tone if the distending force (blood flow or volume) decreases to a greater degree.[7] This may well have occurred in our subjects. It was previously noted that the declines in cardiac outputs were considerably greater in the patients in whom calculated peripheral resistances rose than in those in whom resistances fell, implying that the arteriolar distending force was less in the former patients, contributing to decreases in arteriolar caliber independent of tone. In addition, arterial pressure is ordinarily maintained in the presence of diminished cardiac output by a *compensatory* rise in arteriolar tone (and peripheral resistance). That blood pressures declined in our subjects again suggests that active compensatory arteriolar constriction was impeded by reductions in arteriolar tone.

The declines in pulmonary arterial, pulmonary "wedge," and right ventricular pressures (Group A) appear to have been due to decreases in central blood volumes and cardiac outputs. Pulmonary arteriolar resistances did not change. Significant changes in these pressures were primarily limited to those subjects in whom they were elevated in the control states. This could be explained as a function of the volume-elasticity properties of the pulmonary vessels and heart chambers whose pressure-volume curves are characterized by upward convexities when pressure is plotted on the vertical axis.[18,19] Thus, when pressures are initially normal, changes in volume produce minimal changes in pressure, frequently to such a slight degree as to be within the limits of technical errors in measurement. In contrast, small changes in volume may accomplish large changes in pressures when the latter are initially elevated.

These studies refer to the changes in cardiovascular dynamics during the immediate period (as defined above) after the administration of chlorothiazide. The results do not necessarily relate to effects during long-term drug therapy. However, other investigators suggest that distinct vascular effects play a role probably for as long as the drug is administered.

Summary

The acute effects of chlorothiazide upon cardiovascular dynamics were studied in 10 patients with systemic hypertension and in 2 normotensive subjects. Measurements were made before and after (the immediate postdrug phase) the intravenous administration of chlorothiazide. Fluid balances were also evaluated before and after administration of the drug.

In 7 patients (Group A) significant declines in systemic arterial pressures occurred during the immediate postdrug phase. These patients had pre-existing *hypertension*. In most instances these changes in pressures were due to reductions in cardiac outputs (or stroke volumes). In 3 subjects there were significant declines in total peripheral resistance, suggesting reductions in peripheral arteriolar tone. In 3 others peripheral resistances increased. It is believed that the increased resistances in the latter patients probably were due to passive reductions in arteriolar caliber (as a consequence of reductions in flow) rather than to increases in tone. Central vascular pressures decreased in those subjects in whom they were initially elevated. This appeared to be related to the decreases in cardiac outputs and central blood volumes. Plasma and blood volumes did not change in those patients in whom they were measured. There were no consistent relationships between fluid balances and changes in cardiodynamics.

In 5 subjects (Group B) there were no changes in systemic arterial pressures during the immediate postdrug phases. Three of these patients had pre-existing hypertension and 2 were normotensive. Plasma and blood volumes did not change. Fluid balances were similar to those of Group A.

The data suggest that the mechanisms of the antihypertensive action of chlorothiazide include distinct vascular (vasodilating) effects apart from the role oligemia may have. These vascular effects of the drug appear to depend on the existence of the hypertensive state. The exact nature of these effects are unknown, although various possibilities are discussed.

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Experimental study on ventricular extrasystoles provoked by vagal stimulation

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Carotid sinus pressure occasionally leads[1] to the appearance of extrasystoles. They can be elicited and registered electrocardiographically in some patients during or shortly after carotid sinus pressure, thus confirming a clinical diagnosis. Both experimentally and clinically these ectopic beats are most often of ventricular origin. This is of interest since vagus fibers are said to be nonexistent in the ventricles and vagal effects on the ventricles of the mammalian heart are generally absent. Investigations with the myocardiograph of Cushny[2] and measurements of intraventricular pressure[3] showed no effect of vagal stimulation on cardiac contractility.

An experimental study of the effect of vagal stimulation on ventricular extrasystoles was undertaken on dogs in 1929.[4] A solution of aconitine in distilled water was injected intravenously. Before any change in rate, rhythm, or form of the complexes was noticeable, vagal stimulation regularly elicited the appearance of a bigeminal ventricular rhythm. When the bigeminal rhythm was well established, stimulation of the vagus led to an increase in the number of ectopic beats after a normal complex. This effect was immediate and reproducible. However, it was not possible to generalize from these experiments, since aconitine extrasystoles showed a paradoxical response to other measures. They disappeared promptly on sympathetic stimulation, and their number increased under the influence of choline or potassium. In view of these findings, we undertook the study of the effect of vagal stimulation on ventricular extrasystoles provoked by other substances.

In experiments in which a 20 or 30 per cent solution of sodium chloride was applied locally to the ventricle of the exposed heart of the dog, a paroxysmal ventricular tachycardia appeared which originated in the treated area. The decision was made to study the effect of vagal stimulation on these extrasystoles.

Method

Dogs which weighed between 10 and 15 kilograms were anesthetized with intraperitoneal sodium pentobarbital (16 mg./Kg.) and morphine (5 mg./Kg.). The chest was opened after artificial respiration had been instituted, and the heart was exposed. The right vagus was attached to a shielded electrode. Injection of 0.01 c.c. of a 20 per cent solution of sodium chloride was made into a small area near the surface of the right or left ventricle. The ECG was registered in Lead II.

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Results

In most experiments there was an immediate ventricular tachycardia. This generally subsided within 1 or 2 minutes. To avoid the period during which chance recurrence of the tachycardia was likely, vagal stimulation was not applied during the first 2 or 3 minutes after injection of the salt solution. In some experiments no tachycardia developed after the application of sodium chloride, and in such cases the vagal stimulation elicited the arrhythmia. In most experiments the effects were reproducible. Thus the effect of vagal stimulation seen in Fig. 1 could be elicited five additional times. About 8 to 10 minutes after the end of the tachycardia, vagal stimulation failed to provoke extrasystoles.

Fig. 1 was obtained in an experiment in which an attempt was made to inject the solution of sodium chloride into the area of the atrioventricular node near the coronary sinus vein. This resulted at first in a ventricular tachycardia which was caused by some of the sodium chloride reaching the base of the right ventricle (Fig. 1,*A*). After the tachycardia ended, an atrioventricular rhythm without extrasystoles appeared. Vagal stimulation (Fig. 1 *B*) inhibited this rhythm and elicited groups of bigeminy and trigeminy with the same extrasystoles which caused the preceding ventricular tachycardia (Fig. 1 *B D*). After eleven such groups, atrioventricular rhythm and sinus rhythm reappeared. Renewed vagal stimulation had the same result.

An important fact in these experiments is that the interval between the extrasystoles caused by vagal stimulation is very short (Fig. 2). In this experiment the interval measures 0.16 second, which corresponds to a heart rate of 375 beats per minute. Here, as in other experiments, the extrasystoles disappeared immediately after the end of the stimulation. These characteristics rule out the possibility that these extrasystoles could have been ectopic beats which escaped from the lower centers because of the slowing of the heart. The coupling in our experiments was so short that they could have appeared even if the heart rate had not decreased during vagal stimulation.

Fig. 3, obtained in the course of another experiment, showed the appearance of multiple extrasystoles during vagal stimulation. The extrasystoles caused by the application of sodium chloride without vagal stimulation never exhibited this rapid rate; they would beat at about 180 per minute, whereas after vagal stimulation the rate could become very much faster. In Fig. 3 the interval between the second and third extrasystoles is 0.12 second, corresponding to a rate of 500 beats per minute.

In Fig. 4 the extrasystoles brought out by vagal stimulation appeared in groups. Pairs of ectopic beats are separated by pauses of variable duration. After the end of vagal stimulation at the beginning of Fig. 4 *B* there are multiple extrasystoles coupled to the sinus beats. Again in this instance the interectopic interval and the coupling are such that the abnormal beats could have appeared even if the heart had not been slowed by vagal stimulation.

The same rapid rate of extrasystoles is again in evidence in Fig. 5 after vagal stimulation. In this experiment we see left ventricular extrasystoles as the sodium chloride was applied to the left ventricle.

This effect of vagal stimulation was observed in 11 out of 24 experiments.

Discussion

The results of these experiments show that extrasystoles caused by focal administration of hypertonic sodium chloride reappear during vagal stimulation, usually with a much faster rate. Whereas aconitine extrasystoles which were elicited in a similar manner persisted for a long time after cessation of the vagal stimulation, the extrasystoles in the present experiments disappeared immediately or within a few seconds. There is no doubt that we are dealing with true extrasystoles, that is, with beats elicited by the previous beat. Previous experimental studies on the effect of vagal stimulation and vagal reflexes on the appearance of extrasystoles are discussed elsewhere and will therefore not be analyzed here. We stress only the investigations of Hering, Heymans[6] and Schott on carotid sinus stimulation and extrasystoles in the rabbit. Ventricular extrasystoles may appear or disappear during vagal stimulation and in a previous

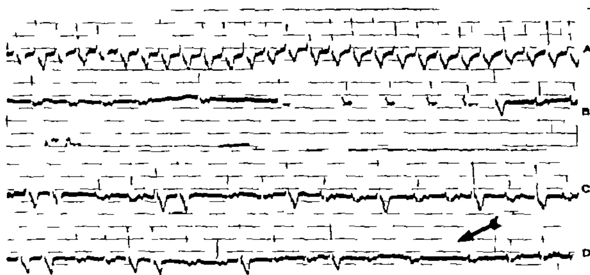


Fig. 1. A shows ventricular tachycardia which appeared after the injection of 0 05 c of 20 per cent solution of sodium chloride into the posterior aspect of the right ventricle near the atrioventricular groove. The rate 1 beats per minute. After the end of the tachycardia an atrioventricular rhythm appeared. Vagal stimulation slowed the rate and sinus rhythm soon reappeared with extrasystoles which followed the preceding sinus beat after a coupling of 0 36 to 0 40 second. The extrasystoles disappeared after a few seconds but reappeared in the same manner during the consecutive stimulations.

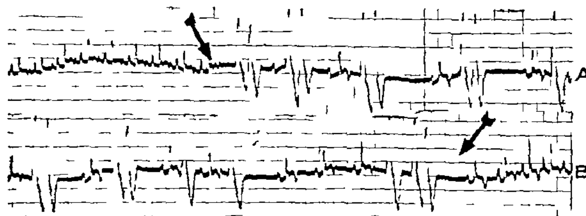


Fig. A and B are continuous tracings. A shows sinus tachycardia of 166 beats per minute. Vagal stimulation lead immediately to the appearance of ventricular extrasystoles in the form of trigeminal groups. The extrasystoles disappear immediately after the end of the stimulation (last part of B). The first extrasystole appears *after a coupling of 0 33 second. It varies in the other beats and is only 0 16 second in B. The distance between* two extrasystoles is as short as 0 16 second which corresponds to a rate of 3 5 beats per minute.

report we demonstrated the reappearance of a ventricular tachycardia upon such stimulation after the application of a 30 per cent solution of sodium chloride to the surface of the ventricle.[1]

Vagal stimulation in the dog elicited similar rapid extrasystoles without premedication at least in one experiment[13] and similar bursts of rapid extrasystoles have been seen in man during compression of the carotid sinus region.[7]

Textbooks generally state that carotid sinus pressure is of no effect in ventricular tachycardias. Although this is usually true there is a well-documented observation reported by Wenckebach and Winterberg[23] in which a ventricular tachycardia could be stopped by carotid pressure. In an other study mechanical irritation of the respiratory tract caused the appearance of ventricular extrasystoles. Carotid pressure or eyeball pressure could pro

voke groups of rapid ventricular extrasystoles[8, 14] or abolish them if they were already present.[1] Even such substances as calcium or potassium will cause or abolish extrasystoles depending on the condition of the experiment.

A stimulating effect of the vagus on ventricular extrasystoles was observed in the dog after intravenous injection of digitalis and after administration of calcium chloride.[11] When a solution of sodium chloride is applied to the atria, vagal stimulation leads regularly to atrial fibrillation.

Vagal effects on ventricular impulse formation and ventricular conduction have been reported in several older observations. Erlanger observed a slight chronotropic effect of vagal stimulation during heart block, and this was confirmed.[10, 17, 9] In man the injection of a choline ester, carbamylcholine chloride, was shown to slow the ectopic rhythm in parasystole[4] and

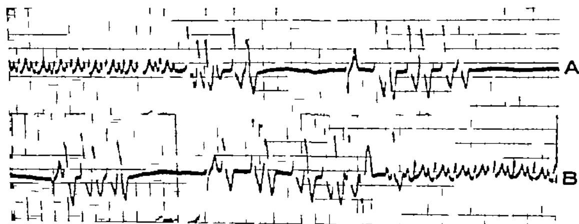


Fig. 3. There is sinus tachycardia with a rate of 214. Vagal stimulation leads to a burst of ventricular extrasystoles with rates up to 500 per minute. After this burst coupled beats appear following after 0.20 second the preceding automatic beat. The first extrasystole follows the preceding sinus beat after 0.40 second.

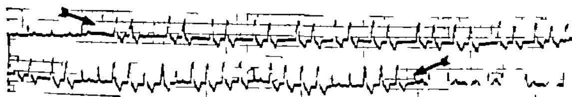


Fig. 4. Vagal stimulation in this experiment caused the appearance of extrasystoles in groups. After the end of the vagal stimulation (first third of *B*) coupled extrasystoles appear followed by sinus rhythm with an occasional atrial extrasystole. The two tracings are continuous.

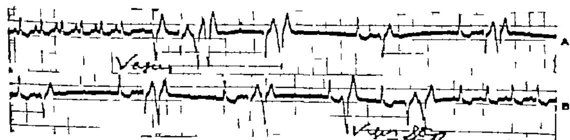


Fig. 5. In this experiment the solution of sodium chloride had been applied to the left ventricle. Here vagal stimulation elicited left ventricular extrasystoles with rapid rates.

we ha e repeatedl observed the lowing of parasy tolic entricular centers by carotid pres ure The i flu nce ot carotid pres ure on bundle branch block ha been discussed by Dressler

The mech m ot the appearance of ventricular extr t les durin agal stim ulation i ot clear Th same phenomenon in the contine experime ts wa explained b the release ot acet lcholine in the atria which led in a sen itized ventricle to an bnormal response to the minute amount ot acet lcholine reaching it[22] Acet lcholine reduces the re tance of membranes and increases the r permeab lity for pota sium Th ma facil tate the appearance of afterpotent ils and therefore of extra sy toles It ma be tated in objection to thi th t extrasystoles are related to ch nges in rate which result from agal stimul tion but in Figs 2 and 3 as well a in se eral other experiments the change in rate the duration of diastole preceding the first extrasy tol was so small that th mechani m is hi hly improbable On the other hand the extras toles appear so earl after the onset of the agal stimu lation th t the amount of acet lchol n reach th entricles from the atria c n only be very small

The complete bsence of il fibers in the mammal an heart ha recentl been denied[15] It is pos ble that uch fibers abundant in the lower cl sses of animal do appear occa ionall an inherited anomaly

The extras toles in the present series of experiments are certainly not provoked by the timulation ot sympathetic fibers which are said to be found occa onally in the vagu nerve Again t thi interpretation peaks their appearance without any latent period immediately after the onset of the vagal stimulation

The extra y toles which appeared durin agal timulation had as the illustrations how the same configuration a that of the extrasy toles which were provoked by the application of sodium chloride They came from the s me focus Minor d fferences in form are caused by the differences in rate The rap d rate of these extrasy toles i noteworthy It wa much higher than that observed in extrasy toles caused by focal application of digitalis trophanthin sodium chloride sodium citrate or oxalate and veratrine

The extrasystoles described in the pres ent tudy follow each other so quickly that it seems possible that one extrasystole appearing during the vulnerable period may lead to ventricular fibrillation and sudden death

Summary

Ventricular extrasystolic tachycardias were provoked by focal application of a hypertonic solution of sodium chloride on the exposed heart of the dog After these extrasystoles subsided faradic stimulation of the right agus nerve made them re appear This effect was reproducible The extrasystoles which were observed during vagal stimulation were identical with those which appeared after the application of sodium chloride A characteristic feature of these extras stoles was their unusually hi h rat

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we have repeatedly observed the slowing of parasystolic ventricular centers by carotid pressure. The influence of carotid pressure on bundle branch block has been discussed by Dressler.

The mechanism of the appearance of ventricular extrasystoles during vagal stimulation is not clear. This same phenomenon in the ... continue experiments was explained by the release of acetylcholine in the atria which led in a sensitized ventricle to an abnormal response to the minute amounts of acetylcholine reaching it. Acetylcholine reduces the resistance of membranes and increases their permeability for potassium. This may facilitate the appearance of afterpotentials and therefore of extrasystoles. It may be cited in objection to this that extrasystoles are related to changes in rate which result from vagal stimulation, but in Figs. 2 and 3, as well as in several other experiments, the change in rate, the duration of diastole preceding the first extrasystole, was so small that this mechanism is highly improbable. On the other hand, the extrasystoles appear so early after the onset of the vagal stimulation that the amount of acetylcholine reaching the ventricles from the atria can only be very small.

The complete absence of vagal fibers in the mammalian heart has recently been denied.[13,14] It is possible that such fibers, abundant in the lower classes of animals, do appear occasionally as an inherited anomaly.

The extrasystoles in the present series of experiments are certainly not provoked by the stimulation of sympathetic fibers which are said to be found occasionally in the vagus nerve. Against this interpretation speak their appearance without any latent period immediately after the onset of the vagal stimulation.

The extrasystoles which appeared during vagal stimulation had, as the illustrations show, the same configuration as that of the extrasystoles which were provoked by the application of sodium chloride. They came from the same focus. Minor differences in form are caused by the differences in rate. The rapid rate of these extrasystoles is noteworthy. It was much higher than that observed in extrasystoles caused by focal application of digitalis, strophanthin, sodium chloride, sodium citrate or oxalate, and veratrine.

The extrasystoles described in the present study follow each other so quickly that it seems possible that one extrasystole appearing during the vulnerable period may lead to ventricular fibrillation and sudden death.

Summary

Ventricular extrasystolic tachycardias were provoked by focal application of a hypertonic solution of sodium chloride on the exposed heart of the dog. After these extrasystoles subsided, faradic stimulation of the right vagus nerve made them reappear. This effect was reproducible. The extrasystoles which were observed during vagal stimulation were identical with those which appeared after the application of sodium chloride. A characteristic feature of these extrasystoles was their unusually high rate.

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given 3 ounces of lipid emulsion (containing egg yolk, soya lecithin, glycerin and pea nut oil) as a source of fat. Eighteen of the individuals in this group were ambulant and were allowed to continue with normal physical activities between each veni puncture. The other 7 subjects rested in bed during the study. The other volunteers (15 healthy subjects and 25 patients with coronary artery disease) took 4 ounces of milk and 4 ounces of "double" cream (i.e. 60 Gm. of fat). All the members of this group, with the exception of 5 healthy subjects, were confined to bed throughout the study as well as for 24 hours before hand. Care was taken to ensure that the entire quantity of fat was consumed on each occasion. Every individual fasted for at least 9 hours before the first specimen of blood was withdrawn, as well as through out the experiment, with the exception of the standard meal of fat.

The clotting time of the blood was determined by the Lee and White method.

Results

It is evident from Tables I and II that the mean values for serum turbidity recorded in the healthy subjects after the administration of sublingual heparin were essentially similar to those obtained during the control experiment, irrespective of whether the lipid emulsion or milk and cream was employed as the source of fat.

Table III demonstrates that there was no significant difference between the mean values for serum turbidity before and after the administration of sublingual heparin in the patients with coronary artery disease.

Comparison of the values presented in Tables II and III indicates that the postprandial turbidity of the serum was more intense and prolonged in the series of patients with ischemic heart disease than in the group of healthy subjects, irrespective of the administration of heparin.

The clotting time of the blood was determined when the subjects were in the fasting state and at 3 and 5 hours post

Table I Average serum turbidity after 3 oz. of lipid emulsion in [illegible] healthy subjects

	Fasting	2 hr	3 hr	4 hr	5 hr	6 hr
Control values	0 041	0 184	0 324	0 278	0 214	0 090
Values after 4,500 I.U. of sublingual heparin	0 043	0 190	0 376	0 264	0 [illegible]03	0 034

*For the sake of brevity, the values for serum turbidity in individual subjects and patients have not been included in the tables of this publication, although they are available on request.

Table II Average serum turbidity after 4 oz. of milk and 4 oz. of cream in 15 healthy subjects

	Fasting	2 hr	3 hr	4 hr	5 hr	6 hr
Control values	0 048	0 [illegible]33	0 4[illegible]4	0 334	0 [illegible]46	0 130
Values after 4,500 I.U. of sublingual heparin	0 044	0 [illegible]40	0 418	0 376	0 258	0 125

Table III Average serum turbidity after 4 oz. of milk and 4 oz. of cream in [illegible] patients with coronary artery disease

	Fasting	2 hr	3 hr	4 hr	5 hr	6 hr
Control values	0 070	0 338	0 550	0 594	0 512	0 3[illegible]4
Values after 4,500 I.U. of sublingual heparin	0 069	0 340	0 534	0 586	0 570	0 385

prandially in 10 of the healthy subjects both during the control experiments and after the administration of sublingual heparin. No significant alterations in the clotting time were recorded in any of the individuals concerned.

Discussion

Previous claims as to the efficacy of sublingual heparin in enhancing the clarification of postprandial lipemic serum could not be confirmed in the present study either in the group of healthy subjects or in the series of patients with coronary artery disease. It seems unlikely that this discrepancy arose as a result of inadequate dosage, for in this investigation each individual received a total quantity of 4,500 I.U. of heparin, whereas Fuller[4] and Shaftel and Selman reported a pronounced effect after the administration of only 1,500 I.U. of this material. Furthermore, the lipid emulsion used as a standard load of fat in 25 of the healthy subjects in the series under review was identical with that employed by these workers. Nevertheless, in the present study the opportunity was also taken to assess the effect of sublingual heparin after a meal which consisted of milk and cream, since a preparation of this type is unlikely to gain acceptance as a fat-clearing agent of practicable value unless it can be shown to promote the clarification of lipemic serum which results from the ingestion of lipids commonly found in the average diet. (The lipid emulsion utilized by Fuller[4] and Shaftel and Selman[5] as well as by the present investigator in 25 of the healthy subjects must be regarded as a highly artificial preparation.)

The failure of sublingual heparin to promote significant clarification of hyperlipemic serum in the present series finds some support from the results published by Engelberg. This investigator measured the plasma lipemic clearing and lipolytic activity of triglyceride in 21 subjects as well as the levels of heparin in the plasma of 13 individuals before and after the administration of 1,500 I.U. of sublingual heparin. A significant degree of absorption was demonstrated in only 3 patients. On the other hand, the administration of even small amounts of intravenous heparin led to a definite increase in the clearing and lipolytic activity of the blood. Engelberg suggested that the divergence between his results and those of Fuller[4] was probably due either to the fat-clearing action of other mucinous polysaccharides contained in the heparin preparation or to the failure of Fuller to use placebo tablets in his control observations.

The absence of a significant alteration in the clotting time of the blood after the administration of sublingual heparin in the present study is in agreement with the results of other workers. According to Engelberg,[7] the failure of even large doses of sublingual heparin to induce an anticoagulant effect[4-] provides additional evidence against any substantial absorption by this route, inasmuch as a recent report[8] suggested that the amount of intravenous heparin required to influence the clotting mechanism is no greater than that necessary for lipemia clearing (except for very small doses below 3 mg.).

Irrespective of the administration of sublingual heparin, however, the present study did reveal that ingestion of a standard quantity of fat has a much more marked effect on the serum turbidity of patients with ischemic heart disease than on that of healthy persons. Although the individuals in this series were not age matched, it may be noted that there was in fact comparatively little disparity in the average age between the two groups of subjects. Reduction of the tolerance for fat in patients with coronary artery disease has likewise been reported by other workers, including Woldow and associates, Barritt, and Mitchell and Bronte Stewart. However, the relevance of these observations in regard to the pathogenesis of coronary occlusive disease must as yet remain conjectural. The mechanism of increased alimentary lipemia in these patients is also far from certain. Thus, according to Block and associates, the heparin-activated enzyme system may well be defective in patients with atheroma. On the other hand, Hood and co-workers,[12] Kaufmann, and Baker[13] were unable to demonstrate any difference in the clearing factor activity between normal control subjects and patients with coronary artery disease. It is of interest, too, that Becker and associates have shown that intra

venous fat disappears from the plasma at the same rate in patients with widely different degrees of alimentary lipemia. Recently Mitchell and Bronte Stewart[11] have suggested that the very intense lipemia which develops in patients with ischemic heart disease depends upon a difference in the rate of absorption of fat in these patients rather than upon a dif ference in the rate of removal

Summary

The lactescence of postprandial serum was measured in 40 healthy subjects as well as in 25 patients with coronary artery disease before and after the administration of sublingual heparin (4 500 I U) Twenty five of the healthy subjects were given 3 ounces of lipid emulsion as a standard load of fat the other individuals received 4 ounces of milk and 4 ounces of double cream (i e 60 Gm of fat)

The average degree of postprandial serum turbidity after the administration of sublingual heparin was not found to differ significantly from that observed dur ing the control experiments either in the series of healthy subjects or in the group of patients with ischemic heart disease

No significant alterations in the whole blood clotting time were demonstrated in 10 healthy subjects who received sub lingual heparin

Irrespective of the administration of heparin ingestion of a standard meal of fat produced a much more pronounced effect on the serum turbidity of patients with coronary artery disease than on that of the healthy subjects

I wish to thank Dr Shirley Smith for allowing me to study his patients with coronary artery disease I am also grateful to the Clinical Research Com mittee of Charing Cross Hospital for providing facilities which enabled this research to be per formed

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Digitalis and the pulmonary circulation

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Although much is known about the effects of digitalis on the heart, the effects on the pulmonary circulation are quite uncertain. In anesthetized dogs the intravenous injection of various digitalis preparations has been shown to cause an increase in pulmonary arterial pressure. On the other hand, subsequent reports on patients who have heart disease and who usually are in heart failure show largely a decrease in pulmonary arterial pressure (see references). These differences may be related to the differences in species or to pre-existing disease states. The effects of digitalis can be defined by a systematic comparison of the following determinants of the pulmonary circulation in human beings and in dogs: (a) pulmonary arterial pressure, (b) pulmonary venous pressure, (c) pulmonary blood flow, and (d) the derived pulmonary vascular resistance. In man the measurements of (b) and (c) and the derivation of (d) are indirect in nature, which necessitates the qualification of conclusions in the investigation of mechanisms. On the other hand, the corresponding techniques in dogs are direct and allow the identification of the various causes for the observed hemodynamic effects of digitalis. The specific effects of digitalis on pulmonary blood flow and pulmonary blood vascular resistance in the dog are described and the role of nervous and non-nervous factors are identified.

Methods

Dogs were anesthetized with morphine (2 mg. per kilogram subcutaneously) and chloralose (70 mg. per kilogram intravenously). The following procedures were routinely performed on all animals: (a) cannulation of the trachea to allow the use of a Starling Ideal Pump, (b) cannulation of a femoral vein for drug injection, (c) catheterization of a carotid artery for recording of aortic blood pressure by a Statham transducer, and (d) opening of the chest in the left fifth intercostal space to allow measurements of pressures in the pulmonary artery and left atrium from catheters tied into the vessels of the left upper lobe. The additional procedures performed in each of two groups of dogs consisted of the following:

1. Measurement of pulmonary venous outflow (8 dogs). This was recorded by a method described previously.[4] All the effluent blood (from the vein of the left lower lobe) was collected in a collapsible rubber reservoir and returned to the in-

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mal's own left atrium or femoral vein by means of a Sigmamotor pump. The pump was manually adjusted to empty the reservoir continuously and this was checked by visual inspection. A Shipley Wilson rotameter was inserted into the outflow side of the pump. The above mentioned system records mean blood flow and does not indicate the pulsatile character of the flow. Manuronate (10 mg per kilogram intravenously) was routinely used as the anticoagulant.

2. Inflow perfusion of the left lower lobe (14 dogs). The artery to the left lower lobe was cannulated and supplied with blood from the dog's own right atrium through a Sigmamotor pump. The perfusion pressure was recorded by means of a side arm attached to a Statham transducer.

The following digitalis preparations were injected either intravenously (femoral vein) or directly into the perfused pulmonary artery: acetyl strophanthidin (0.025 to 0.075 mg per kilogram), digoxin* (0.1 mg per kilogram), and ouabain (0.035 mg per kilogram). Denervation of the lungs was accomplished by combined bilateral cervical vagotomy and excision of the 4 upper thoracic sympathetic ganglia. In some dogs atropine sulfate (1 mg per kilogram) and bretylium tosylate† (5 mg per kilogram) were used for selective blockade of the parasympathetic and sympathetic nerves, respectively.

Results

Pulmonary arterial blood pressure. The typical effect of acetyl strophanthidin is depicted in Fig. 1. Within 2 minutes after the intravenous injection of 0.05 mg per kilogram there was a slight fall in systemic blood pressure and pulmonary arterial pressure. The subsequent behavior of both pressures for the same dog is shown in Fig. 2, which also shows that both pressures do not run parallel. The systemic pressure rises in a few minutes but the pulmonary arterial pressure remains low. This fact serves to emphasize the dissimilarities in control between the systemic and pulmonary circulation and more of this will be discussed below.

*Supplied by Dr. K. K. Chen, Lilly Research Laboratories.
†Supplied by General J. Wood, Burroughs-Wellcome Laboratories.

A total of 5 intact dogs was tested and the results are summarized in Table I. Four dogs showed a fall in pulmonary arterial pressure and one showed no change. The lack of consistency of fall in all dogs could not be explained on the basis of this group of dogs, but became understandable when the perfusion experiments were completed. It is important to point out here that the fall in pulmonary arterial pressure (encountered in 4 out of 5 dogs) is strikingly similar to the observations in man. The similarity also includes the appearance of bradycardia, but not the other measurements, which are discussed in subsequent paragraphs.

Fig. 1. Intravenous injection of acetyl strophanthidin causes a reduction in pulmonary arterial pressure and pulmonary venous outflow. Subsequent changes are shown in Fig. 2.

Fig. 2. Summary of effects of acetyl strophanthidin in the same dog depicted in Fig. 1, plotted over a longer period. Note the similar effect of the glycoside and of bleeding on pulmonary arterial pressure, blood flow, and vascular resistance.

Table I Results obtained from dogs with intact innervation and 3 other dogs

Dog no. Fig	Experimental	Mean systemic blood pressure mm Hg	%Δ	Heart rate /min	%Δ	Mean pulmonary arterial blood pressure mm Hg	%Δ	Mean atrial blood pressure (mm Hg) Left	Right	Pulmonary venous flow ml/min	%Δ	Pulmonary vascular resistance P/F	%Δ
13	C tr l	100		130		23		5		330		0.0607	
	Ac l pha th lm 0.0 5 3 min	1	+75	90	−30	15	35	4 5		120	−64	0.125	+81
13	(1)	)		200		21		7		220		0.09	
	Ac l t p an h l 0.0 min	100	+3	140	−30	21	0	5		155	−30	0.135	+4
1	C r l	13		1(2		22			2 2	210		0.104	
	Ac l tr phan hd 0.05 4 m	14	+	8(	−4	1(	−2		2 1	120	42	0.133	+26
1	C n l	103		1 6		18			5	230		0.078	
	A t l phen h l (0 min	9	−	133	31	1	−		(	160	−30	0.106	+3(
1(	C l	115		192		21			7 5	190		0.11	
	Ac h hd (0 4 m	1	−10	113	−41	20	−			12	−3	0.16	+45
	A era %Δ		+4		−31		−14				−40		+46
18	A t n (l	10		72		0			11	320		0.062	
	Acetyl t h th lin 0.0 m	185	+	205	−6	19	−5		10	255	−20	0.075(	+19
14	Heart l n (control)	135		84		1			10	305		0.114	
	Act l ha il l 0.0 (m	150	+11	50	−40	)	−17		12 5	155	−4	0.18	+64
15	I act ners	1 0		180		1(		5		0		0.05	
	Di min 0.1 (30 min	12	−4	13(	−32	15	−(			2	−1(	0.0(	+11

Left atrial pressure. It is necessary to consider first the outflow side of the lung when the cause of a fall in pulmonary arterial pressure is under consideration. The left atrial pressure was measured in 3 dogs and a fall of 0.5 to 2 mm. was noted. However, the intensity of fall in pulmonary arterial pressure is larger by 1 mm. Hg or more, so that one can conclude that the fall in left atrial pressure may contribute to the fall in pulmonary arterial pressure but is not the exclusive cause.

Pulmonary venous blood flow. A more important cause for the fall in arterial pressure in the lungs is the reduction in blood flow, which averaged 40 per cent. Experiments were then conducted to detect whether the reduction in pulmonary blood flow was entirely due to cardiac slowing. One dog was vagotomized prior to the administration of acetyl strophanthidin and another dog after its administration. Cardiac slowing induced by digitalis disappeared, but the reduction in flow still occurred even when acetyl strophanthidin was injected into the ascending aorta. All these observations exclude two causes for the reduction in pulmonary blood flow: cardiac slowing and interference in venous return induced by stimulation of cardiac receptors which induce peripheral vasodilatation, a mechanism that has been proposed by Melville. Another explanation, a direct action on systemic vessels to reduce venous return, was not directly proved.

Pulmonary vascular resistance. This factor was calculated by simply *dividing* pulmonary arterial pressure by pulmonary venous flow. No correction for changes in *venous* pressure was required because the pulmonary venous outflow was collected at the same level as the left atrium and was kept constant. In 5 intact dogs acetyl strophanthidin caused an increase in calculated vascular resistance (mean +46 per cent). One previously vagotomized dog also showed a similar increase. One additional dog was subjected to chemical sympathectomy by bretylium and the subsequent injection of acetyl strophanthidin still caused an increase in pulmonary vascular resistance. The results obtained from these 2 dogs indicate the increase in pulmonary vascular resistance. Two possibilities remain: (a) local action of digitalis on the lung vessels and (b) passive response to a reduction in blood flow. The former could not be tested by simple measurements of blood flow but was studied by lung perfusion (see below). Factor (b) was investigated in the same dogs in which pulmonary blood flow was measured.

Passive increase in vascular resistance induced by bleeding. To evaluate the effect which reduced pulmonary blood flow itself (induced by acetyl strophanthidin) had on pulmonary vascular resistance, we compared the effects of the drug with those of reduction in flow by bleeding. In 2 dogs such a reduction in circulating blood volume by 7 ml. per kilogram caused a reduction in pulmonary blood flow and an increase in vascular resistance (Fig. 2). This increase could be elicited even after digitalization and even after bretylium. The similarity between the increase in pulmonary vascular resistance induced by acetyl strophanthidin and that induced by bleeding suggests that the reduction in pulmonary blood flow is a cause for the drug-induced increase in vascular resistance, but this does not necessarily exclude a local action of the drug on the pulmonary vessels.

Pulmonary vasoconstriction of the perfused lung. The perfusion experiments were performed primarily to administer the drug directly into the pulmonary artery. The next group of experiments consisted of perfusion of the left lower lobe with the animal's own mixed venous blood. A typical response is depicted in Fig. 3, in which acetyl strophanthidin is injected directly into the left lobar artery perfused at a constant flow. There was a slowly developing rise in pulmonary arterial pressure which reached its peak 3 minutes after injection. Several other observations should be considered before one can conclude that the increase in perfusion pressure is due to local vasoconstriction.

A. Since alcohol (47.5 per cent, 1 ml.) was used as the solvent for acetyl strophanthidin, alcohol alone was injected as a control procedure, and this did not produce a significant rise in perfusion pressure.

B. The corresponding vein of the perfused left lower lobe remained intact so that, although the drug initially reached the perfused lung, it subsequently reached the left atrium and the systemic circulation. The behavior of the left atrial pressure should be considered as a possible cause for the rise in pulmonary arterial pressure. The left atrial pressure either decreased, was unchanged, or rose much less than did the pulmonary arterial pressure.

C. Because of its systemic effects, acetyl strophanthidin can influence the lungs through its vagal or sympathetic innerva

Fig 3 Injection directly into the left lower lobe perfused at a constant flow The initial bump in the perfusion pressure is an injection artifact but the delayed rise is due to acetyl strophanthidin and is accompanied by no change in left atrial pressure This record does not include the pulmonary arterial pressure of all the other lobes which are supplied by the dog's own right ventricle

Fig 4 Summary of denervation procedures on the pulmonary vasoconstriction induced in the perfused lung by acetyl strophanthidin 0 0 mg per kilogram. Note that the vasoconstrictor response occurred even when perfusion pressures were abnormally higher than normal values

tion The perfused lung experiment was therefore performed on 14 dogs with a combination of one or two of the following cervical vagotomy thoracic sympathectomy and intravenous injection of bretylium (Fig 4) These procedures did not interfere with the ability of acetyl strophanthidin to induce a rise in pulmonary arterial perfusion pressure

D The increase in vascular resistance induced by acetyl strophanthidin was demonstrated also when the flow to the perfused lobe was intentionally increased or decreased In each of 5 dogs a pressure flow curve was derived before and after digitalis It can be noted from Fig 5 that prior to the drug the perfused lobe demonstrated the passive decrease in resistance to an intentional increase in flow Two or three control runs resulted in reproducible pressure flow curves After acetyl strophanthidin a similar curve was derived but at a higher level than the control There is therefore an increase in vascular resistance at all levels of flow tested and denervation did not influence this effect of acetyl strophanthidin

E It has been demonstrated recently that the *pulmonary venous junction* to the left atrium can be constricted by certain foreign agents[7] This possibility was tested by measuring pressures separately in the pulmonary vein and left atrium in 6 dogs Acetyl strophanthidin did not cause a gradient between these two although the pulmonary arterial pressure increased (Fig 6)

Digoxin and ouabain These two glycosides were tested in 2 dogs Digoxin (0 1 mg per kilogram) caused a reduction in pulmonary blood flow and pulmonary arterial pressure but an increase in pulmonary vascular resistance (last dog in Table I) Ouabain (0 035 mg per kilogram) injected directly into the perfused lobe caused local pulmonary vasoconstriction

Discussion

The recent availability of a rapidly acting glycoside acetyl strophanthidin has allowed the investigation of the effects of digitalis in the pulmonary circulation of the dog Because the methods used were of a direct nature which involved vessel cannulation perfusion rotameters and accessory tubings the effects of the drug must be distinguished from spontaneous deterioration of the preparation The experiments reported above establish the following actions of acetyl strophanthidin on the pulmonary circulation

1 Acetyl strophanthidin causes a *local* vasoconstriction of the perfused lung This is based on the rise in perfusion arterial

pressure at a constant flow or on a uniformly higher perfusion pressure at varying flows after the injection of the drug The exact location of the constriction has not been detected except that the pulmonary venous-left atrial junction can be excluded In 1914 Macht[4] showed that the medium sized branch of the pulmonary artery of pigs and oxen was constricted by various digitalis preparations

2 The increase in pulmonary vascular resistance induced by a local vascular action of acetyl strophanthidin cannot be easily demonstrated by a rise in pulmonary arterial pressure if blood flow is not kept constant In the intact dog the pulmonary arterial pressure is reduced because of an immediate reduction in pulmonary blood flow *In such situations the calculation of* pulmonary vascular resistance shows an increase after the drug but it is not possible to attribute this increase to local action because of the passive effect of reduction in flow It is necessary to explain why earlier investigators [3] noted a rise in pulmonary arterial pressure after the intravenous injection of strophanthin digitoxin or digitalin It is probable that the longer latent period resulted in an initial predominance of local vasoconstriction over a delayed reduction in pulmonary blood flow The use of a rapidly acting glycoside in the experiments reported above caused an early predominance of the latter As long as digitalis can elicit opposite actions on vessels (constriction) and flow (to reduction) a change in either direction can be expected

3 Several possible nervous mechanisms can be excluded as a cause for the observed effects of acetyl strophanthidin on the pulmonary circulation Bradycardia which follows digitalization is not an essential accompaniment for the reduction in pulmonary blood flow because vagotomy does not alter this hemodynamic effect of digitalis The cause of the reduction in flow appears to be a local action on the systemic vessels and this has been adequately studied by other investigators The increase in pulmonary vascular resistance in either the intact animal or in the perfused lung could also be elicited even after sympathectomy or by blockade with bretylium This drug has been shown to block the pulmonary vasoconstrictor nerves to the lung vessel [11] so that one can safely conclude that activation of the sympathetic nervous system is not an important mechanism of the rise in pulmonary vascular resistance

The foregoing conclusions refer to the lung of the dog but the situation in the lung of the normal human being is quite uncertain Digitalization in patients with



Fig 5 Pressure-flow curves of perfused lung at varying flow Note higher resistance values after acetyl strophanthidin for the same flow values prior to the drug Only one control run is depicted but two successive control runs resulted in essentially similar pressure curves

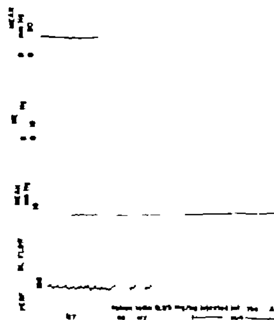


Fig 6 Failure of acetyl strophanthidin to elicit a gradient between the pulmonary vein and the atrium

congestive heart failure, cor pulmonale, or mitral stenosis has varied effects on the pulmonary circulation, but the majority of patients show reduction in calculated vascular resistance (see bibliography in Reference 4). If there is local vasoconstriction in the lung of the human being, it is obscured by other factors. An increase in cardiac output usually accompanies the reduction in resistance in the lung of the human being; therefore, such reduction is probably a passive response to the increase in flow. Also, with improved function of the left heart and resulting fall in pulmonary venous pressure, there is an apparent fall in pulmonary vascular resistance. Clarification of these possibilities will have to await additional studies in which more direct methods are used to calculate vascular resistance in dogs which are in heart failure and in patients.

Summary

In anesthetized dogs the intravenous injection of acetyl strophanthidin caused a slight decrease in pulmonary arterial pressure which could not be explained by the effect on left atrial pressure. There was a marked decrease in the pulmonary venous flow, which was often accompanied by cardiac slowing, and an increase in the calculated pulmonary vascular resistance. The cause of the increased pulmonary resistance is a combination of (a) the passive nature due to the decreased blood flow and (b) local vasoconstriction of the perfused lung. The performance of vagotomy and thoracic sympathectomy and the intravenous injection of bretylium excluded nervous factors as a cause of the vasoconstriction.

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The effect of ouabain on cardiac automaticity in reserpine-pretreated dogs

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One of the effects of a toxic dose of ouabain is an increase in cardiac automaticity which results in ventricular ectopic beats Recently it has been suggested that the increase in cardiac automaticity caused by ouabain may be due to the release of catecholamines from the heart[1] This suggestion was based on the observation that ouabain usually produced spontaneous beating in the isolated papillary muscle from an untreated cat but did not cause spontaneous beating in the isolated papillary muscle from cats pretreated with doses of reserpine sufficient to deplete the heart of catecholamines The amine involved would most likely be norepinephrine[2]

This study was undertaken to determine whether catecholamines are involved in the mechanism by which ouabain causes ventricular ectopic beats in the dog

Methods

Mongrel dogs of both sexes anesthetized with pentobarbital sodium (30 mg per kilogram intravenously) were used in the experiments The heart rate and rhythm were determined from electrocardiograms (Standard Limb Lead II) The myocardial contractile force was obtained by means of a Walton strain gauge arch sutured to the surface of the right ventricle A Sanborn pressure transducer was connected to a carotid artery to measure the blood pressure The lungs were artificially ventilated by means of a Palmer pump A femoral vein was cannulated for the injection of compounds Recordings of the blood pressure electrocardiogram and contractile force were made with a Sanborn multichannel recorder

An aqueous solution of ouabain was used and each dog received the drug according to the following schedule an initial dose of ouabain 40 μg per kilogram was injected after which additional doses of 20 μg per kilogram were given every 15 minutes until the appearance of ventricular tachycardia which was observed for 10 to 15 minutes before the experiment was terminated

The dogs were divided into three groups One group of 6 dogs received only ouabain A second group of 6 dogs was pretreated with reserpine (0 5 mg per kilogram intraperitoneally) once a day for 2 days and was tested on the third day The reserpine was made up as a 1 per cent solution in 20 per cent ascorbic acid as the solubilizing vehicle A third group of 3 dogs was pretreated with dichloroisoproterenol (DCI)[3] A dose of 5 mg per kilogram was injected intravenously 10 to 15 minutes before the first dose of ouabain was given The data were analyzed according to the methods of Mainland[4]

From the Department of Pharmacology McNeil Laboratories Inc Fort Washington Pa
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[3] Supplied by Dr Irwin H Slater Lilly Research Laboratories Indianapolis Ind

Table I. Response of the heart to ouabain in normal and reserpine pretreated dogs

Dog number	Control: Ventricular rate (beats/min.)	Control: Contractile force (mm.)	Control: Cardiac rhythm	Total dose of ouabain (µg/Kg.)	After ouabain: Ventricular rate (beats/min.)	After ouabain: Maximum increase in heart rate (%)	After ouabain: Maximum increase in contractile force (%)	After ouabain: Cardiac rhythm
Normal dogs								
1	160	11.0	SR	80	240	50	36	VT†
2	140	7.0	SR	60	240	71	57	VT
3	140	9.5	SR	80	220	57	84	VT
4	200	10.0	SR	80	220	10	60	VT
5	160	11.0	SR	60	240	50	100	VT
Mean	160	9.7		72	232	47.6	67.4	
S.E. Mean‡	±11.1	±0.75		±5.0	±5.0	±10.3	±11.3	
Reserpine pretreated dogs								
1	130	9.5	SR	80	200	54	58	VT
2	130	7.0	SR	80	220	70	157	VT
3	120	10.5	SR	80	220	83	100	VT
4	120	11.0	SR	100	200	67	45	VT
	100	8.0	SR	100	200	100	75	VT
Mean	120	9.2		88	208	74.8	87	
S.E. Mean	±5.6	±0.76		±5.0	± 0	±7.9	±20.1	

SR Sinus rhythm
†VT Ventricular tachycardia
‡S.E. Mean [illegible]

Results

Control dogs. Ouabain 120 µg per kilogram in divided doses caused a complete auriculoventricular block in one dog and resulted in an idioventricular rhythm that was followed by cardiac arrest. Ventricular tachycardia was produced in 5 dogs after cumulative doses of ouabain which ranged from 60 to 80 µg per kilogram. Ouabain also increased the myocardial force of contractions. The results are summarized in Table I.

Reserpine pretreated dogs. Ouabain produced effects on the rhythm and contractile force of the heart in the reserpine pretreated animals which were similar to the effects produced by ouabain in the control group. Cardiac arrest preceded by a 4 to 1 auriculoventricular block was obtained in one dog after a total dose of 140 µg per kilogram of ouabain. Ventricular tachycardia occurred in 5 dogs after cumulative doses of ouabain which ranged from 80 to 100 µg per kilogram were given. There was no significant difference ($0.02 < p < 0.05$) between the mean dose of ouabain required to establish ventricular tachycardia in the control animals and that in the reserpine pretreated dogs. The mean increase in myocardial contractile force was greater in this group than in the control group; however, the difference was not statistically significant ($0.4 < p < 0.5$). The results are summarized in Table I.

DCI pretreated dogs. Ventricular tachycardias which were of the same intensity when judged by rate as those in the control and reserpine pretreated dogs were produced in dogs which were pretreated with DCI (5 mg. per kilogram intravenously). The dose of ouabain required to establish the arrhythmia ranged from 60 to 80 µg per kilogram. DCI was shown prior to the injection of ouabain to markedly reduce or abolish the positive inotropic and chronotropic effects of isoproterenol (1 µg per kilogram). A second injection of 5 mg. of DCI per kilogram was

made during the course of the ventricular tachycardia The compound had little or no effect on the existing rate or rhythm of the heart in two tests In one test a bout of sinus tachycardia which lasted for less than 30 seconds was observed after the injection of DCI This was not considered to be a significant change DCI alone produced increases in the sinus rate and myocardial force of contractions The maximum increases in the heart rate due to DCI in these 3 dogs were 16 37 and 83 per cent of the control value and the maximum increases in the myocardial contractile force were 17 36 and 53 per cent of the control value

Discussion

The results of this study suggest that the mechanism by which ouabain causes ventricular ectopic beats in the anesthetized dog is not dependent on the release of catecholamines from the heart adrenal medulla or stores which mediate the response of adrenergic nerves to the heart and certain other sites Ouabain in essentially the same doses produced ventricular tachycardia in the control group as frequently and of the same intensity when judged by rate as in dogs in which the heart adrenal glands and stores subserving the action of several adrenergic nerves have presumably been depleted of catecholamines by reserpine[5] This suggestion is further supported by the fact that pretreatment of dogs with DCI which has been reported to inhibit ventricular tachycardia caused by epinephrine or norepinephrine[8] did not alter the frequency of appearance of ventricular tachycardia in these tests and did not diminish the rate of the ventricular tachycardias which were produced Furthermore the injection of DCI during the tachycardia had little or no effect on the arrhythmia The results of the experiments utilizing DCI are however complicated by the fact that DCI alone possesses sympathomimetic actions on the heart which were observed in these tests and reported by Moran and Perkins

The results also suggest that the increase in myocardial force of contractions produced by ouabain is not due in part to the release of catecholamines as suggested by Cairoli and co workers[1] and Tanz[9] since the ability of ouabain to increase the myocardial force of contractions was not inhibited in dogs pretreated with reserpine however the experimental conditions between these tests and those of Cairoli and co workers and Tanz are so widely divergent that any attempt at a possible explanation of this apparent discrepancy would be purely speculative

Summary

The findings reported in this study suggest that the increase in cardiac automaticity and the increase in myocardial contractile force due to ouabain are not dependent on the release of catecholamines from the heart adrenal glands or stores which mediate the response of certain adrenergic nerves

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Case reports

Pulmonary atresia with intact ventricular septum
Report of two cases studied by selective angiocardiography and right heart catheterization

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In 1956 Greenwold and collaborators reported that cases of pulmonary atresia with intact ventricular septum could be divided into two groups: those in which a tiny or small right ventricular cavity (Type 1) was manifest and those in which there was a right ventricular cavity of large or normal size (Type 2). They suggested that these two groups could be differentiated on the basis of roentgenographic and electrocardiographic data. Recently Davignon and collaborators reported on 20 cases and further differentiated the two groups by means of similar criteria. They noted that in patients who are more than 1 week of age the correct diagnosis can usually be made on these grounds but suggested that selective angiocardiography from the right ventricle should serve in doubtful cases to establish the diagnosis and differentiate the types with accuracy. We have recently studied 2 patients with pulmonary atresia and intact ventricular septum by means of catheterization of the right side of the heart and selective angiocardiography. One of these patients had a right ventricular cavity of small size and the other had a large right ventricular cavity.

It is the purpose of the present report to describe these 2 cases in detail, emphasizing the hemodynamic and roentgenographic differences between the two types as demonstrated by right ventricular angiocardiography and right heart catheterization.

Report of cases

Case 1† A 10-day-old white boy was hospitalized because of the history of a cardiac murmur and moderate cyanosis since birth. Cardiac enlargement had been noted on roentgenologic examination when he was 3 days old. The mother's pregnancy had been normal and the family history was noncontributory.

Physical examination showed a well-developed irritable white boy with Grade 2 (on a basis of 1 to 4) generalized cyanosis. No thrill was felt on palpation of the precordium. The second cardiac sound was thought to be single in the pulmonary area. A Grade 3 (on a basis of 1 to 4) continuous murmur was present and was heard best at the upper left

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†This case was briefly referred to in a previous publication.

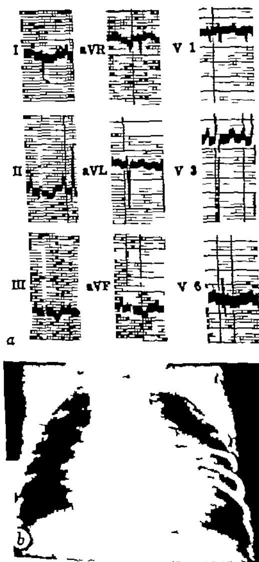


Fig 1 Case 1 Electrocardiogram made when the patient was 10 day old howing evidence of right trial enlargement and left entricular dominance for this patient age (see text) *b* Anteroposterior thoracic roentgenogram showing pronounced car diac enlargement Note unusual prominence of the border of right side of heart Pulmonary va culature is decreased

sternal border the systolic component appeared to be harsher predominated t the pex and extended toward the left axilla The lungs were clear The ed e of the liver palpable t the right co tal margin The femoral pulses ere of good quality The remainder of the physical examination wa noncontributory

The electrocardiogram showed alternating p riod f sinus and nodal rhythm The QRS xis was +100 degrees The presence of peaked P w ves ind cated right trial enlargement The configuration of the QRS complexes in the standard and unipolar ex tremity lead s w ll in the precordial lead in dicated left ventricular dominance for inf t of thi age A interesting hift of the I xis the frontal plane w also noted the axi w −100 degree w th inverted T w es in lead I II III and V and upright T es i Lc I aVa nd V (Fig 1)

A roentgenog am of the thora howed cardiac largement with prominent right border of the heart and decreased pulmonary v cular re (Fig 1)

Four day after adm ion the patie t wa ex mined by means of combined right heart catheteri zation and angiocardiography For th purpose local nesthetic agent was adm n tered w thout premedication The data on pre ures and oxyge sat ration of the blood obtained at that time are ummarized T ble I The sy tolic pre sure in the right v tricle wa higher than that in the femoral artery The en l-diastolic pres ure in the right en tricle as ormal The right and left trial pre sures re similar magnitude and the contou of the right trial pulse normal There was desaturation of femoral arterial blood which re sulted from the presence of a large right to-left hunt t the trial level as show by the low satura tion in the left trium and by indicator-dilutio curves The oxygen capacity of the blood w 2 ml per 100 ml

Indicator-dil tion curves were recorded at the femoral artery after injection of 5 mg of Cardio-Green Dy curve 1 recorded after injection f the indicator int the right entricle demon trated n ppearance time of approxim tely 3 second large initial deflection and ery slow clearance of dye from the circulation Dy curves 2 nd 3 made after the injection to the nferior en ca nd left atrium re pect ely were simila t curv 1 except for the 3 second ppearance times nd more rapid build up phase These curves ndicated the presence of large right to-left shunt w th the passage of dy to the pulmonary scular bed oc curring downstream to the left trium The dy jected int the right ent cle obviously cleared from this chamber with con iderable rapidity indicating that the blood in the right entricle ex changed freely th the principal circulation Study of the time components did not perm t us to say hether exchange occurred back ard through the tricu pid al or forward through the abnormal myocardial sinusoid which were present

Table I Hemodynamic data in Case 1 (small ight ventricle—Type I)

Site	Pressure (m Hg)	Oxygen saturation (%)
Femoral artery	85/42 to 70/42	6
Right ventricle	130/4 to 13	42
Right trium mid	14/2†	27 to 46
Left trium	14/3†	73
Superior ena ca	—	31
Inferior ena cav	—	24 to 43

By av tt ann †

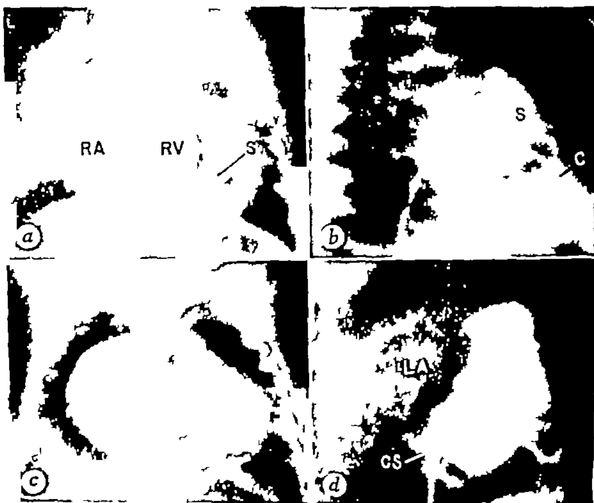


Fig 2 Case 1 1*b* Angiocardiogram made w th injection int right entricle (*RV*) Catheter ha rebounded so that some of the contrast medium has entered the right atrium (*RA*) Right tricular cavity is tremely mall Myocardial sinusoids (*S*) re well isualized Note the nom l us coronary el (*C*) which at ne cropsy wa found to comm nicate with the myocardial sinusoi ls *c* and *d* Film ma le late n the same series T p of catheter has no w rebounded completely into the right trium In lateral view the left atrium (*LA*) is now f intly opacified by w y of the trial septal defect Reflux fill ng of oronary sinu (*CS*) from right atrium has occurred

An an iocardiogram w ma le th the njection of 5 ml f Diodrast into the right entricular cavity in 1 second w thout disturbance in cardiac hythm In both anteroposterior and lateral views a right ventricular ca ty of sm ll size could be seen clearly the early films Some opacification of the right ventricular wall wa noted (Fig 2) this resulted from filling of the bnormal myocardial sinusoi l which occur in most cases of pulmonary atresia w th intact entricular sept m of Type I A pulmonary outfl w tract or a pulmonary artery wa not seen After the first few films and for the greater part of the jection the cathet r recoi led into the dil ted right atrium The left trium wa also dized later Contrast medium remained in the right ventricular cavity and in the myocardial sinusoi ls until the end of the series

Certain enlarged ventricular (11 per cent) and 4 ulcerate (37 per cent)

Because the locus of entry of the me lium int the pulmonary rt ry could not be determined a secon l angiocardiogram w made 30 m l ter through the left trium (Fig 3) t which the th et r had bee ad anced through n ter tri l communication The same mount of opaque me d um was injected in 1 5 second The left tri l ppendix retained contrast medium throu hout th sequence The left cavities of the heart w re w ll visualiz l the left entricle appeared to be slightly larger than rm l in diastole The aorta w opacified a l this wa f llowed almost im mediately by opacification of the right l left pulmonary rteries the pulmo ary vessel were presumably filled through a patent ductus arteriosu although thi struct re w never cle rly s hown possibly because of superimposition of the left atrial appendix On none of the films could t main pulmonary artery be seen with certainty (Fig 3)

A diagnosis of pulmonary atresia with intact ventricular septum was made although the type was not specified. Because the condition of the infant was deteriorating rapidly, a Brock procedure was attempted the day after cardiac catheterization. Through a stab wound in the right ventricular wall a steel probe was forced into the pulmonary artery and then a curved clamp was introduced and opened rather widely with its tip in the pulmonary artery. Because of the small size of the heart it was not possible to be absolutely certain of these various manipulations. At the completion of the procedure the heart action became slower and weaker and progressed to complete standstill with no response to any of the usual resuscitative measures.

Necropsy revealed that the right atrium was extremely large. A patent foramen ovale was present, partially covered by a redundant remnant of the valve. The right ventricular cavity was small and the right ventricular wall, which were extremely thick, contained numerous small sinusoid and a large anomalous vessel which originated near the apex of the heart and curved upward to anastomose with the anterior descending coronary artery (Fig. 4). The tricuspid orifice was small and the leaflets of the tricuspid valve were somewhat thicker than normal but there was no shortening of the chordae tendineae and the valve appeared to be competent. There was no outflow tract from the right ventricle; its cavity terminated blindly approximately 4 or 5 mm. below the atretic pulmonary valve. The pulmonary artery was about half the size of the aorta. The left ventricle was of good size and the left cavities of the heart appeared to be normal. It was apparent that the surgical tract from the right ventricle had entered the left ventricle at the root of the aorta and had not entered the pulmonary artery as we had thought at the time of operation. The atretic pulmonary valve was intact. The ductus arteriosus was large and widely patent. Microscopic section of the right ventricular wall showed a few regions of fibrosis scattered throughout the myocardium.

Case 2. A 1-day-old white boy was admitted to the hospital because he had had persistent cyanosis and fluttering heart since birth. The mother's pregnancy had been normal; the delivery had been uncomplicated and the birth weight of the child was 5 pounds 11 ounces (2,580 grams). Physical examination showed a small active baby who was moderately cyanotic but in no distress. No thrill was felt over the precordium. The heart sounds were of good quality. The second cardiac sound was thought to be single and a Grade 4 harsh systolic murmur of long duration was heard along the left lower sternal border. A soft murmur of brief duration was heard in late diastole. The peripheral pulses were of good quality. The edge of the liver was palpated 2 cm. below the right costal margin; it was not pulsatile.

The electrocardiogram showed normal sinus rhythm. Extreme right axis deviation was present; the QRS axis was −170 degrees. The configuration of the P waves indicated atrial enlargement. The QRS complex was 0.10 second in duration and indicated delayed activation of the right ventricle which was consistent with dilatation of that chamber (diastolic or volume overloading). The left ventricular patterns were normal (Fig. 5 *a*).

A roentgenogram showed that the cardiac silhouette was considerably enlarged, especially in the region of the right atrium. The vascularity of the lungs was decreased (Fig. 5 *b*).

Because of increasing cyanosis and gradual deterioration of the patient's condition, a definitive diagnosis was considered necessary and cardiac catheterization was undertaken the next day. The procedure, performed without anesthesia, was

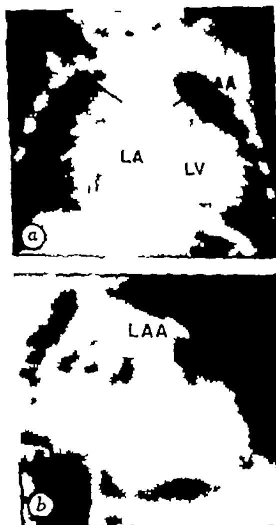


Fig. 3. Case 1. Anteroposterior (*a*) and lateral (*b*) angiocardiograms made with injection of contrast medium into the left atrium. The left atrium (*LA*) and its appendage (*LAA*), the left ventricle (*LV*), and the ascending aorta (*A*) were opacified in that order. Immediately after opacification of the ascending aorta the pulmonary arteries were opacified presumably by way of a patent ductus arteriosus, although the ductus itself was never visualized because of superimposition of the opacified left atrial appendage. Cavities of the left of the heart are of normal size.

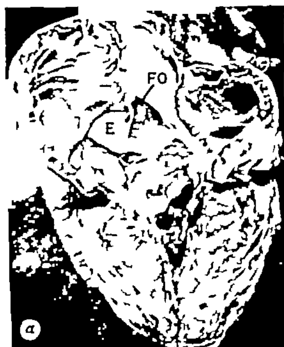




Fig 4 Case 1 Ri ht side f heart h ing lar ri ht trium nd mall right entricular ca t O probe w passed from the left trial side through the pate t foramen oval (FO) Anothe probe w pa sed from the inferior ena cava t the r ht trium t demon trat the large F tach n s l e (F) b Close up iew of right entricular wall howin si nw l (S) nd nmalous coronary essel (CV) pr bes are p cal portion f thi essel

limited in scope The data on pres ures a l oxy en saturation of the bl od are gi Table II The pres ure tracing from th right atrium bowed prominent wa e which w con iste t w th some degree of tricu p l regur tation. The pressure in the ri ht ventricle ormal for thi ch m ber and wa gnif cantly less than that n the left ventricle nce pulmonary atresia a present these pressures can be explained on the ba of

sev re tricuspid regurg tation or fa lure of the right entricle The oxyge saturation of blood from the left entricle was approximately 40 per ce t but the degree of saturation of samples of blood draw from the right side of the heart showed considerable ariation possibly because of the precarious cardio-scular condition of the patient

For the angiocardiogram 4 ml of Diodrast w jected to the outflow tract of the ri ht tricle The ri ht entricle was thus walled enormously dilated and occupied the great r part of the left portion of the cardiac lhouett The right trium filled from the right entricle because of the presence f se ere regurgitation throu h the tricu pid al Thus l appeared to be situated more t the l ft han normal The right trium and it appendage w re also greatly dil ted the right atrial appendage occupied mo t of the heart hadow anteriorly and t the right of the pinal column The right ve tricle ended as a blind pouch directly under the pr t m t which th pulmonary l usually see N the the main pulmonary art ry and pulmonary l nor the left tricle nd left tri m ere ualized (Fig 6)

The diag s pulmonary atresia w th intact tric lar septum nd l rge ri ht ventricle (Type A Brock procedure wa carried out few hours af the catheterization The right trium nd right trick ere greatly d lated The great vessel re mall oment d The main pulmonary art ry as pproximately half the size of the aorta At t ri the pulmonary artery narrow d t form a firm tretic essel few millimeters in length A tab wound was made low the right entricle and throu h this poi ted knife wa inserted t w rd the pulmonary art ry On two occasions it passed through the obstructed segment int the pulmonary artery A mall Brock dilator was forced along the same path y but t w tremely dif l It t be certain th t the instrume t had passed th gh the bstruct d se ment Finally a Lott basket d lat w pa sed int the heart but be a ttempt w made t force it to the pulmonary art ry the dilat r emer ed f om the ri ht ve tricle adjacent t the pulm nary al ular ring which

Table II Hemodynamic data in Case 2 (large ight ventricle Type 2)

Site	Pres (mm Hg)	Oxygen saturation (%)
Femoral artery	Not tere l	—
Left entricle	67/7	41
Left trium	8†/−3	42 t 54
Ri ht ventricle	28/8	20 t 28
Right atrium m l	71/2	37
I fer r ena cav	—	29
Superi r ena cav	—	17

[illegible]

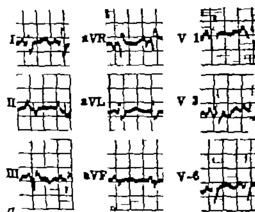




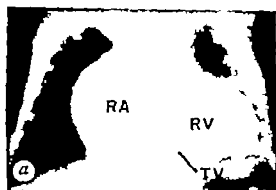
Fig Case 2 Electrocardiogram taken when the patient was 1 day old Note large P waves and evidence of delayed activation of the right ventricle (see text) *b* Anteroposterior thoracic roentgenogram showing extreme cardiac enlargement with pronounced enlargement in the region of the right atrium Pulmonary vasculature is decreased

resulted in some bleeding A suture closed this defect satisfactorily but cardiac action deteriorated rapidly and finally ceased All attempts to restore cardiac action failed A postmortem examination was not made

Comment

In pulmonary atresia with intact ventricular septum the patients are usually severely ill cyanotic infants The great majority die before the age of 3 months If the patients are more than 1 week of age the two types of this cardiac defect can usually be differentiated on the basis of clinical electrocardiographic and roentgenographic findings Those infants with a right ventricular cavity of small size (Type 1) will in general show moderate cardiac enlargement on the roentgenogram of the thorax and evidence of right axis deviation left ventricular over and atrial hypertrophy on the electrocardiogram Those with a right ventricular cavity of normal size or larger (Type 2) will show pronounced cardiac enlargement on the roentgenogram of the thorax and evidence of right ventricular hypertrophy right atrial enlargement and right axis deviation with good but not abnormal left ventricular potential on the electrocardiogram In our experience these criteria usually do not apply to patients who are less than 1 week of age in younger patients the picture is atypical because the described roentgenographic and electrocardiographic features have not yet developed

Hemodynamically Type 1 and Type 2 cases are quite different In cases of Type 1 the tricuspid valve although small is usually normally formed and appears to be competent Once the blood is in the right ventricle it has no ready path of egress and may be forced under high pressure





F Case 2 Angiocardiogram made with injection of contrast medium into right ventricle (RV) Ventricular systole *b* Ventricular diastole Dense opacification of the right atrium (*RA*) has occurred because of the presence of tricuspid insufficiency Right ventricular cavity large The tricuspid valve (*TV*) lies to the left of its usual

through abnormal myocardial sinusoids[3] These sinusoids are thought to be persistent embryologic channels which have been kept open by the high right ventricular pressure which prevails throughout fetal and early postnatal life They communicate by abnormal vessels with the coronary vascular system The angiocardiogram in Case 1 suggests that the dye is forced through these myocardial sinusoids and from there in a retrograde fashion into the coronary circulation Clearance of dye from the ventricular cavity is slow Indicator-dilution curves are not specific The observed prolongation of the time components of the right ventricular curve could have been the result of slowed clearance either in a backward (via the tricuspid valve) or in a forward (via the sinusoids) direction Militating against the presence of severe tricuspid insufficiency in Case 1 were the normal contour of the right atrial pressure and the presence of a pronounced elevation of right ventricular systolic pressure It has been suggested recently that in these cases a regurgitant tricuspid orifice prevents the obstructed ventricle from becoming obliterated by stasis thrombosis

In cases of Type 2 the tricuspid valve is usually grossly malformed and obviously incompetent The blood is driven back and forth across it during the cardiac cycle Tricuspid insufficiency is the main factor in dilatation of the right ventricular cavity In approximately half of the cases the appearance of the tricuspid valve resembles that seen in an Ebstein malformation The leaflets are elongated and partially fused to the right ventricular wall or the ventricular septum These facts are well demonstrated by the angiocardiogram in Case 2 The thin walled large ventricular chamber is seen clearly as is the evidence of gross regurgitation through the tricuspid orifice The tricuspid valve is displaced more to the left than is normal This image could well have been caused by the aforementioned malformation of the valve The hemodynamic data were not remarkable in this case except for the low right ventricular pressure which is an obvious consequence of gross tricuspid insufficiency

In cases of Type 1 the extent of the muscular obstruction in the atretic right ventricular outflow tract makes any attempt at surgical correction by means of a Brock procedure unlikely to succeed Furthermore the capacity of the small right ventricle may not be sufficient to accept a normal pulmonary flow at least in the early postoperative phase this would make a Brock procedure even if technically successful hemodynamically ineffective

Creation of a Blalock or a Potts anastomosis would certainly seem to be the most effective way of providing the necessary flow of blood to the lungs in these cases However such procedures are technically difficult in small infants and the usual precarious condition of these patients increases the hazard of any operation In cases of Type 2 the large right ventricular cavity usually extends directly under the atretic valve a thin membrane separates the ventricular cavity from a usually adequate pulmonary artery In theory at least a Brock procedure is more likely to be successful in such a case However in the presence of the wide orifice of an incompetent tricuspid valve the right ventricle may be incapable of building up enough pressure to force blood in significant quantity through the small opening created by the Brock procedure In such cases an operation to provide a shunt may have a greater chance of success but the problems posed by this group of cases are major ones At present direct visualization of the defect with the use of extracorporeal circulation would certainly seem to be the method of choice but we have not attempted this type of treatment to date Although these considerations do not induce an optimistic outlook with regard to surgical treatment and the mortality due to operation in such cases has been extremely high surgical intervention seems justified because of the natural course followed by patients with this malformation who are not treated surgically

Summary

Two cases of pulmonary atresia and intact ventricular septum have been presented In one case a right ventricular cavity of small size was present (Type 1) and in the other a right ventricular cavity large size was found (Type 2) The 1 defect had high and normal

contour of atrial pressure. Injection of opaque medium into the right ventricular cavity demonstrated anomalous myocardial sinusoids. The patient with the Type 2 lesion had a normal right ventricular pressure and a dominant v wave in the contour of the right atrial pressure curve. An angiocardiogram showed a large dilated right ventricular cavity, gross tricuspid regurgitation, and a tricuspid valve displaced to the left. The surgical implications of these findings were discussed briefly.

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through abnormal myocardial sinusoids.[8] These sinusoids are thought to be persistent embryologic channels which have been kept open by the high right ventricular pressure which prevail throughout fetal and early postnatal life. They communicate both with normal vessels with the coronary vascular system. The angiocardiogram in Case 1 suggests that the dye is forced through these myocardial sinusoids and from there in a retrograde fashion into the coronary circulation. Clearance of dye from the ventricular cavity is slow. Indicator-dilution curves are not specific. The observed prolongation of the time components of the right ventricular curve could have been the result of slowed clearance either in a backward (via the tricuspid valve) or in a forward (via the sinusoids) direction. Militating against the presence of severe tricuspid insufficiency in Case 1 were the normal contour of the right atrial pressure and the presence of a pronounced elevation of right ventricular systolic pressure. It has been suggested recently that in these cases a regurgitant tricuspid orifice prevents the obstructed ventricle from becoming obliterated by atrium thrombosis.

In cases of Type 2 the tricuspid valve is usually grossly malformed and obviously incompetent. The blood is driven back and forth across it during the cardiac cycle. Tricuspid insufficiency is the main factor in dilatation of the right ventricular cavity. In approximately half of the cases the appearance of the tricuspid valve resembles that seen in an Ebstein malformation. The leaflets are elongated and partially fused to the right ventricular wall or the ventricular septum. These facts are well demonstrated by the angiocardiogram in Case 2. The thin-walled large ventricular chamber is seen clearly, as is the evidence of gross regurgitation through the tricuspid orifice. The tricuspid valve is displaced more to the left than is normal. This image could well have been caused by the afore-mentioned malformation of the valve. The hemodynamic data were not remarkable in this case except for the low right ventricular pressure, which is an obvious consequence of gross tricuspid insufficiency.

In cases of Type 1 the extent of the muscular obstruction in the atretic right ventricular outflow tract makes any attempt at surgical correction by means of a Brock procedure unlikely to succeed. Furthermore, the capacity of the small right ventricle may not be sufficient to accept a normal pulmonary flow, at least in the early postoperative phase; this would make a Brock procedure, even if technically successful, hemodynamically ineffective.

Creation of a Blalock or a Potts anastomosis would certainly seem to be the most effective way of providing the necessary flow of blood to the lungs in these cases. However, such procedures are technically difficult in small infants, and the usual precarious condition of these patients increases the hazard of any operation. In cases of Type 2 the large right ventricular cavity usually extends directly under the atretic valve; a thin membrane separates the ventricular cavity from a usually adequate pulmonary artery. In theory, at least, a Brock procedure is more likely to be successful in such a case. However, in the presence of the wide orifice of an incompetent tricuspid valve, the right ventricle may be incapable of building up enough pressure to force blood in significant quantity through the small opening created by the Brock procedure. In such cases an operation to provide a shunt may have a greater chance of success, but the problems posed by this group of cases are major ones. At present, direct visualization of the defect with the use of extracorporeal circulation would certainly seem to be the method of choice, but we have not attempted this type of treatment to date. Although these considerations do not induce an optimistic outlook with regard to surgical treatment, and the mortality due to operation in such cases has been extremely high, surgical intervention seems justified because of the natural course followed by patients with this malformation who are not treated surgically.

Summary

Two cases of pulmonary atresia and intact ventricular septum have been presented. In one case a right ventricular cavity of small size was present (Type 1) and in the other a right ventricular cavity of large size was found (Type 2). The patient with the Type 1 defect had high right ventricular pressure and a normal

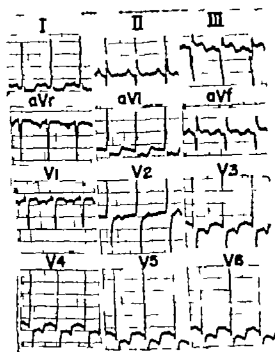


Fig 1 Electrocardiogram of May 19 1959 hows abnormal Q es and S-T nd T w changes in Leads I II III nd V diagnostic of diaphragmatic myocardial infarction Tall R w es in Lead 1 nd V and over the left precordium re compatible with left entricular hypertrophy

An electrocardiogram taken on adm ion (Fig 1) howed tall R waves in Leads V and V with S-T egment and T e changes in the left precord al lead compatible ith left entricular hypertroph nd strain I addition changes con istent with diaphragmatic myocardial infarction ere present in Lead II III and V

A chest ra film (Fig 2) revealed some er all increa e in the size of the heart w th left entricular enlargement and changes indicat of pa n con gestion in both lung bases

Urinalysis was negativ The hemoglobin was 1 8 Gm per cent and the whit blood cell count was 11 100 with 70 per cent neutroph ls The erythrocyte sedimentation rate was 24 mm in one hour (Wintrobe) The bloo l urea nitrogen as 35 mg per cent nd the blood sugar as 85 mg pe cent Blood culture was negativ and the Eagle flocculation test for syphilis was also negati

Subsequent course He w put t bed d gitalized given Diuril and low salt diet H improved con iderabl on th reg men and w d charged on June 1 1959 receiving digitalis nd 500 mg of Diuril daily Electrocard ograms on the second and twelfth day after hospitalization revealed no essen tial change from the tracing recorded t the time of dmis ion

At home he deteriorated rapidly H became short of breath and developed edema of the legs and sc rotes. Because he de eloped nausea and d gital was discontinued T weeks

ch n j ndice fir t noticed and thi gradual became worse Palpit tion became m re se ere nd he be t complain f angin t rest

The patie t w readmitted t hospital on J 1 6 1959 Physi al examination rev led m ked j ndice and orthopnea The neck ei were gros ly di tended Respiration were labored t a rat of 38 per minute The bl d pres ure w 155/100 mm Hg nd the arterial pulse w 100 pe mi t and irreg lar the temperature w nor m l There ere si g of pleural effu ion t both l ng l se nd moi t râles were he rd l l terally The ardiac findin were unchanged from those t the time of the pre ou hospitalizat on The abdomen w prot berant t nd scites w s present together th gros edema of leg sacrum nd scrot m

A el trocardiogram (Fig 3) re eal d general decre se in amplitude of the QRS complexes ov the left precordium nd numerou premat re en tricular beats The changes Leads II III and V were again compatible w th old d phrag m tic myocardial infarction A chest ray film taken week after dmi ion revealed a further increase in the ize of the heart together w th ele tion of the right dome of the diaphragm cc t t w th hepatomegaly

Pertinent laboratory result The white bl od cell count was 15 000 w th a normal differential The blood urea nitrogen as 138 mg pe cent SGOT was 14 unit Serum bilirubi w 3 0 mg pe cent (direct 1 8 mg) pl ma albumin 4 1 Gm an l globulin Gm Alkaline pho ph t se was 6 2 Bodan ky nits Th mol turbidity was 4 5 nit The serum sodium was 1 5 mEq pe liter hloride 90 mEq pota ium 3 9 mE and the carbon dioxide combining power mEq pe liter

Although he howed slight initial improvement fter ten treatment for congestiv heart f ilure he oon became ref actory t such treatment and died 26 da after adm on



Fig 2 The chest ray film reveal changes indica tiv of pass v congestion in both lung bases with er all increase in heart size and left enlargement

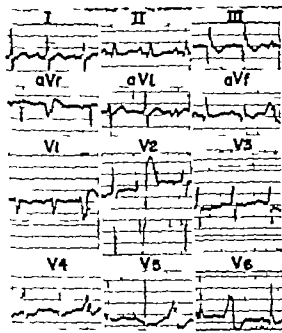


Fig. 3. Electrocardiogram of July 1, 1959, shows the appearance of numerous premature ventricular beats and generalized decrease in amplitude of the QRS complexes.

Necropsy report. Gross examination revealed bilateral pleural effusion, pericardial effusion, and ascites.

The heart weighed 5? grams. On the posterior surface of the left ventricle near the mitral valve (Fig. 4) ... thin walled aneurysmal sac which ... 3.5 cm. in diameter and 2 mm. in thickness. The left ventricle elsewhere measured 13 mm. in thickness. In the upper third of the interventricular septum (Fig. 5) was ... acquired interventricular septal defect which measured 1.8 cm. in diameter. The edges were smooth and were surrounded by dense scar tissue. The area of myocardial scarring around the septal defect was continuous with the wall of the cardiac aneurysm. A mural thrombus was attached to the wall of the right atrium. There was complete occlusion of the right coronary artery 3 cm. beyond its ostium by organized thrombus. Elsewhere the branches of the right coronary artery contained large arteriosclerotic plaques which almost occluded the lumen. The left coronary artery and its branches were patent.

Microscopic examination. Multiple sections of the heart revealed extensive areas of fibrosis, most marked subendocardially. No evidence of inflammation or recent infarction was noted. Sections of the occluded right coronary artery revealed recanalized sclerotic thrombus with no fresh clot. The edge of the interventricular septal defect and the wall of the aneurysm were formed by dense scar tissue.

Discussion

Two of the serious complications which may result from acute myocardial infarction are rupture of the heart and formation of an aneurysm.

Rupture of the heart occurs in about 10 per cent of the patients with myocardial infarction,[4] and in 1 to 2 per cent such a rupture occurs through the ventricular septum. The incidence of aneurysm after myocardial infarction is generally reported to be about 10 per cent.[11, 12-14]

Rupture of the heart, whether through the septum or the ventricular wall, occurs through areas of myomalacia cordis and usually happens within 2 weeks of infarction.[3] Not infrequently the necrotic area forms an aneurysmal dilatation, and it is through this dilatation that rupture occurs. Rupture is very rare[1, 2, 4, 6] once scar tissue has developed completely (some 3 months after the infarction).[3] In various large reported series of cardiac aneurysms late rupture is not listed as a cause of death.[?] With regard to acquired ventricular septal defects[1, ?, 16, 17] rupture takes place through necrotic muscle whether accompanying acute aneurysmal dilatation is present or not.

The case described presents the unusual feature of perforation of the septal part of a chronic ventriculo-septal aneurysm through scar tissue 8 years after the original



Fig. 4. Photograph of the diaphragmatic surface of the heart showing the ventricular part of the aneurysm bulging at the base of the left ventricle.



Fig 5 Show the entire entriculo-septal aneurysm and perforation as viewed from the left entricular ca ity

infarct with no clinical or pathologic evi dence of more recent infarction

Anticoagulants persistent elevation of the blood pressure after infarct and early physical activity are factors which are be lieved to increase the incidence of cardiac rupture[3] In this instance the onset of symptoms referable to septal perforation occurred during severe physical exertion The blood pressure of the patient on one occasion only was recorded as 158/100 mm Hg but this degree of hypertension seems to be insufficient to have played a part in the cardiac rupture although it might have had some bearing on the forma tion of the aneurysm

Survival after septal perforation which follows myocardial infarction is on the average 7 4 days although there have been exceptional cases of long survival[11] The patient reported upon here survived 10 weeks from the apparent time of septal perforation

Finally an unusual feature of the case described is the development of a ventriculo septal aneurysm after occlusion of only the right coronary artery the left coronary artery remained patent This suggests that the distribution of the branches of the coronary arteries in this patient may have been unusual

Summary

The clinical and pathologic findings are presented from a patient with an acquired ventriculo septal aneurysm and rupture of the interventricular septum The unusual features of the case are (1) rupture of the septum through scar tissue 8 years after the original infarct (2) relatively long survival (3) lack of correlation between the location of the aneurysm and the actual coronary pathology found at necroscopy indicating perhaps an unusual distribution of the coronary artery branches

We wish to thank Dr Richard E Rowall who gave us valuable help and suggestions in the writing of this paper and Dr Bradley Kurg from the Department of Pathology Maryland General Hospital Baltimore Md who made available the necroscopy material

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Clinical pathologic conference

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Clinical abstract

This 20-year-old Negro woman was admitted to the Charity Hospital of Louisiana on May 7 1959 for cardiac operation.

The patient was first seen in 1956 She had been well until approximately 3 years before when she noted easy fatigability and inability to play as heartily as her schoolmates These symptoms began gradually over a period of several weeks to months At that time she developed shortness of breath after only very moderate exertion Her symptoms were very mildly but definitely progressive from the time of onset There were no previous symptoms suggestive of rheumatic fever and there was no history of previous cardiac examinations

The physical and laboratory findings in 1956 and during the 3 years that she was followed in the outpatient cardiac clinic were as follows Blood pressure in the arms was 95/40 mm Hg Physical examination gave essentially negative findings except for the heart The point of maximal impulse was in the fifth intercostal space 2 cm lateral to the mid-clavicular line There was an extremely loud harsh diamond shaped systolic murmur loudest in the aortic area but also heard in the neck at the apex and over the left posterior thorax There was a loud pulmonic second sound which was not split An electrocardiogram showed marked left ventricular hypertrophy (Fig 1) Fluoroscopy and chest x-ray films revealed 3 to 4+ left ventricular enlargement and questionable right ventricular enlargement (Fig 2) The aorta was small and difficult to identify The pulmonary segment was normal There was no definite atrial enlargement The easy fatigability of the patient continued to progress but there were no symptoms suggestive of congestive heart failure

In January 1957 a blowing diastolic murmur was noted at the base and a third heart sound at the apex with a diastolic rumble There was no accentuation of the first heart sound and no opening snap In March of that same year the patient was found to be anemic and in view of the changing murmurs a diagnosis of subacute bacterial endocarditis was considered However numerous blood cultures were negative The anemia which was later attributed to bleeding of the gums due to poor dental hygiene responded slowly but significantly to oral iron therapy The patient was maintained during the next 2 years on penicillin for prophylaxis of rheumatic fever

In February 1959 cardiac fluoroscopy was repeated specifically to search for calcification of the aortic valve however none was seen In March 1959 right and left heart catheterization was performed A systolic gradient of approximately 100 mm Hg across the aortic valve was demonstrated when the catheter was pulled back from the aorta into the left ventricle The operator was of the opinion that the changes in pressure probably represented aortic valvular stenosis without subaortic stenosis No significant diastolic gradient across the mitral valve was detected Because of the severe left ventricular hypertrophy and progressive symptomatology it was decided to attempt to correct the lesion surgically



Fig 1 Electrocardiogram (III is Lead III taken during deep inspiration)

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Fig 2 Erect posteroanterior ra   of the chest Cardia   lhouette outlined

The blood p es ure at the time that the patient was la t hospitalized was 100/60 mm Hg The remainder of the physical examination ga   nega ti e finding except for the examination of the heart which bowed   normal mus rhythm absent aortic second sound and   loud harsh diamond-shaped yst ic murmur over the aortic area accompanied b   palpable thrill A very soft high pitched dia tolic blowing murmur wa   again heard   t the base but no   pical rumble   detected

Hosp ,al course On M   21 1959 an open heart operation w th extracorporeal circulation wa   pe formed The pump-oxygenator was used for   bout 30 minutes   nd the patient seemed t   tolerat   this ell After the procedure however bleeding beg   t mam   ites   nd the bl od pres ure fell   \ te t for acti ation of fibrinol   w   positive She was treated l   inf sion   f l norepinephrine   l re ceived   total of 30 Gm of fibrinogen and 50 mg of prednisolone intravenously over a period of several hours In an attempt t   replace the exten n loss of blood a total of 30 pints of blood was given in the operating room Although the bleeding never topped completely the thora   was closed and the patient was sent to the recovery room Upon her arrival there the peripheral pulse could not be de tected and the blood pressure could not be meas ured The heartbeat was regular Several hours later   igns of pulmonary edema appeared   nd the patient died

Clinical discussion

DR LOVE There are two important aspects of this patient s illness The first is the primary diagnosis and the second is the cause for her failure to survive oper ation This seems to be a straightforward case of aortic stenosis but we must look for clues to other possible lesions

The patient first began having symptoms at the age of 14 years when she noted that she was unable to keep up with her play mates and was more easily fatigued The onset of the fatigability was said to be gradual over a period of several weeks to months This makes it seem genuine She noted shortness of breath after very moder ate exertion This is not a common early sign of disability caused by aortic stenosis Syncope on exercise is common but real dyspnea is more suggestive of the onset of congestive heart failure which is usually



Fig 3 Interior view of left entricle and aorta showing the recent surgical incision   nd the aortic alvular and subvalvular steno   (rrow)



Fig. 4 Close up view of left ventricle and aortic valve showing the valvular and subvalvular stenoses (*arrow*)

a comparatively late manifestation Her symptoms were definitely progressive Therefore this was not a static or trivial lesion but one which produced significant and increasing disability In 1956 the blood pressure was 95/70 mm Hg which is an extremely low pulse pressure and it is difficult to accept this as being truly representative of the usual situation over that 3 year period Most patients with aortic stenosis do not have such a low pulse pressure except during the terminal phases of their illness We can ask ourselves whether the growth and development of this patient would have been normal if she had had congenital aortic stenosis since early infancy The answer is yes In collected groups of patients the degree of physical development was found to be essentially normal in most cases of uncomplicated congenital aortic stenosis

There was a loud harsh diamond shaped systolic murmur heard best at the aortic area but radiating into the neck and to the apex This is of course typical of aortic stenosis A loud pulmonic second sound was heard This is difficult to evaluate Why should there be a loud second sound to the left of the sternum? Was it because the aortic second sound was soft or because of some coincident disease?

The first electrocardiogram in 1956 showed that marked left ventricular hypertrophy was already present at that time Over the course of 3 years there were only minor changes in the tracings I don t see anything in the electrocardiogram to suggest right ventricular hypertrophy Fluoroscopy



Fig. 5 View of mitral valve area showing the thickened and fused chordae tendineae



Fig 6 Photomicrograph of left entricular myocardium show my cardial h pertroph o nttitial fibrosis nd a schoff body (arrow)

rev aled 3 to 4+ l ft e tricul e l r e ment and slight nterior bul e of the ri ht ventri le Right ventricul r enlarge ment a loud pulmonic se ond sound and the murmur suggestive of mitral steno is which w s he rd later would go together w ll but a light anterior bulge of the right entricle n the presence of a m ssive left ventricle i an uncert in sign indeed since the left ventricle dominates the heart hadow and the right ventricle is but a mall appendage on its anterol teral surface The aortic knob w is said to be small and hard to identify The aortic knob in aortic stenosis is charact ristically small Another common roentgenologic finding which i not mentioned in the protocol is a dil itation and anterior promi nence of the ascending part of the aorta This is the most consistent fluoroscopic finding in aortic stenosis The pulmonary segment was norm l and there was no atrial enlargement These findings would certainly be unu u l in mitral tenosis and also in mitral insufficiency which i another possibility The patient s ymp toms of fati ability continued to progress but there were no definite symptoms of congestive heart failure There w is no angina or syncope on effort These are two very common and ominou symptoms in aortic stenosis In January 1957 it w is noted that there was a high pitched decrescendo diastolic murmur at the base Such a murmur would usually originate from the pulmonary or aortic valve Pre sumably it was from the aortic valve in this case although it could have been due to pulmonic insufficiency caused by mitral stenosis There w is a third heart sound at the apex with the diastolic rumble We would need to know the exact timing and character in order to evaluate it It could have been a normal third heart sound a gallop an opening snap or if sy tolic an ejection click The latter is heard at the apex in many patients with mild aortic tenosis In March of that same year it w is noted that the patient was anemic

This might have been the cause of the diastolic apical rumble which w is de scribed In February 1959 cardiac fluoros copy w is carried out to look for calcifi cation in the aortic valve since the patient w is in the a group in which calcium often begins to be deposited in the abnormal aortic valve however no calcification w is seen In the younger age groups calci fication is unusual whatever the etiology When patients reach 30 years of age a majority have calcium in the valve whether the lesion is congenit l or rheum tic In

any case no calcium was seen in this valve In March 1959 a maximal systolic gradient of about 100 mm Hg was demonstrated to exist across the aortic valve establishing the presence of some type of obstruction in the outflow tract Physical examination on the last admission showed an absent aortic second sound Statistically this is an unusual finding in aortic stenosis[1,2] although it is a traditional belief that the aortic second sound is absent in this lesion This is essentially all of the data available and we will try to make a preoperative diagnosis The diagnosis of mitral stenosis will have to be eliminated because there was no good clinical evidence to support the diagnosis and because no gradient between the left atrium and the ventricle was detected at catheterization There are a number of different anatomic conditions which could produce the drop in pressure in the aortic area and it would be helpful to the surgeon to know which one he might be called upon to deal with The stenosis may be in the aorta above the normal valve this is rare[4] It may be valvular which is the most common type It may be below the valve in the ventricle this is not uncommon and occurs in approximately 20 per cent of the patients with congenital aortic stenosis[3]

Another rare syndrome which has been described is that of muscular stenosis of the left ventricular outflow tract This lesion is particularly important to the surgeon since all of the signs of aortic stenosis may be present yet in the heart quiet at operation a finger can be readily introduced through the aortic valve into the apex of the ventricle The stenosis is presumably caused by a functional ring produced by the contraction of the ventricular muscle during systole Our differential diagnosis rests primarily between valvular and subvalvular aortic stenosis Another possibility is bicuspid aortic valve This produces a systolic murmur and frequently a diastolic murmur but it does not alone produce this type of ventricular hypertrophy It is not ordinarily a very significant lesion from a dynamic point of view Another possibility is mitral insufficiency It is not always possible to distinguish between the murmurs of mitral insufficiency and those of aortic stenosis particularly when the two coexist The murmur of aortic stenosis may resemble the murmur of mitral insufficiency when the aortic second sound is delayed and the pulmonary second sound comes at the end of the aortic systolic murmur The differentiation between valvular and sub

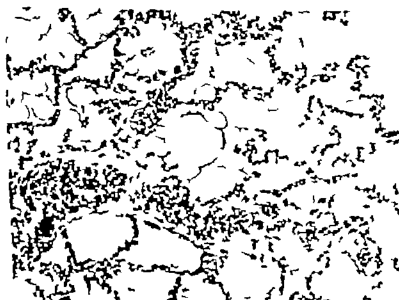


Fig 7 Photomicrograph of lung showing pulmonary thrombi The thrombi are very ca



Fig 4 Ph t micrograph of left entricular m ocardium showing n yo cardial h pertroph ter t tial fibro and an Aschoff body (x ec)

reve led 3 to 4+ left ventricul r enlarge ment and slight anterior bulge of the ri ht entricl R ght ventricular enl rge m nt a loud pulmonic second sound and the murmur suggesti e of mitral stenosis which w s heard later would go together well but a slight anterior bulge of the right v ntri le n the presenc of a m ssive l ft ventricle is an un ert in sign indee l since the l ft ventri le dominates the heart shadow and the right ventricle is but a small appendage on its anterol teral surface The aortic knob w s said to be small and hard to identify The aortic knob in aortic stenosis is characteristically small Another common roentgenologic finding which i not mentioned in the protocol is a dilat ition and anterior promi nence of the ascending part of the aorta This is the mo t con istent fluoroscopic finding in aortic stenosis The pulmonary segment was normal and there was no atrial enlargement These findings would certainly be unusual in mitral stenosi s a d also in mitral insufficiency which is another pos ibility The patient s symp toms of fatigability continued to progre but there were no definit ymptoms of congestive heart failure There was no angina or syncope on effort These are two very common and ominous symptoms in aortic stenosis In January 1957 it was noted that there was a high pitched decrescendo diastolic murmur at the base Such a murmur would usually originate from the pulmonary or aortic valve Pre sumably it was from the aortic valve in this case although it could have been due to pulmonic insufficiency caused by mitral stenosis There was a third heart sound at the apex with the diastolic rumble We would need to know the exact timing and character in order to evaluate it It could have been a normal third heart sound a gallop an opening snap or a systolic in ejection click The latter is heard at the apex in many patients with mild aortic stenosis In March of that same year it was noted that the patient was anemic

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Fig. 8. Photomicrograph of pulmonary vessel showing occlusion of the lumen by a cellular thrombus.

aortic ring there is a slightly roughened plaque which extends into the anterior aortic sinus. The recently sutured incision is seen beginning beside the plaque and extending cephalad. Fig. 4 is a close view of the aortic ring showing the subvalvular stenosis (arrow) and the scarred and fused aortic cusps. Fig. 5 also shows part of the left ventricle including the mitral valve. The valve leaflets are opaque and the chordae tendineae are thickened and fused giving a picture compatible with healed rheumatic valvulitis. There is also some thickening and opacity of the endocardium of the left atrium suggesting a healed mural endocarditis. Fig. 6 is a photomicrograph of the myocardium. There is variation in the size of muscle fibers with nuclei that are enlarged and irregular in shape compatible with hypertrophy of the myocardium. There is a striking and diffuse increase in interstitial fibrous tissue throughout the left ventricle. In addition one small Aschoff body (arrow) is present which contains characteristic Aschoff cells. This is good evidence of a recently active rheumatic myocarditis. Fig. 7 is a photomicrograph of a section of lung and demonstrates the probable cause of death and possibly the cause of generalized bleeding. An abundance of small recent thrombi scattered diffusely throughout all sections examined. The thrombi are located for the most part in the lumina of small and medium sized arteries. They are composed predominantly of leukocytes but some fibrin is present in all instances. The fibrin can be identified sometimes in scattered individual clumps but regularly in the form of delicate networks extending between the formed elements of the clot. The cause of this remarkably diffuse thrombosis of the pulmonary vessels is not apparent but its effect could scarcely fail to be a severe depletion of circulating fibrinogen. It is probable that much of the fibrinogen administered to the patient was promptly fixed in the pulmonary thrombi and failed to reach the systemic circulation. Fig. 8 shows thrombi in the pulmonary vessels and also shows fairly prominent pulmonary congestion. The vessels are somewhat thickened and show adventitial fibrosis. Fig. 9 is a high power view that shows the endothelial swelling which is very prominent in some sections and the fibrillar material representing fibrin. The renal glomeruli present an interesting finding (Fig. 10). There are dilated glomerular capillaries which are completely bloodless and a fat stain of these reveals that there has been fat

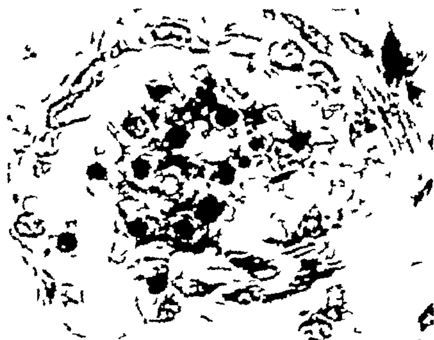


Fig. 9. Photomicrograph of pulmonary vessel showing endothelial cells in old thrombus with poorly formed fibrin network.

ation. These emboli do not occur in great numbers but are easy enough to find. As a result of this finding, fat stains were done on sections of lung and here too fat emboli are present.

In summary, this patient has several lesions. She has both valvular and subvalvular aortic stenosis. The subvalvular lesion is generally considered to be congenital and is sometimes associated with congenital aortic stenosis. It would be difficult to rule out congenital origin in this case. However, the patient has definite evidence of fairly extensive rheumatic heart disease with both a myocarditis and valvulitis. Therefore, I think it is very likely that the aortic valvular stenosis had a rheumatic basis. An inflammatory basis for the subaortic stenosis as well cannot be excluded.[7] In addition there are extensive pulmonary thrombi. I don't know why they formed. Neither do I know whether the clinical shock preceded or followed the intrapulmonary thrombosis. There may have been some local condition in the lung that favored coagulation of blood and the sequestration of fibrin. Certain experiments on intractable shock may explain in part the coagulation of the blood in the lungs and the subsequent appearance of fibrinolysins.[11] Crowell produced intractable shock in association with hypercoagulable blood by bleeding dogs and maintaining hypotension for prolonged periods. The hypercoagulable state was associated with intravascular clotting and pulmonary emboli. Hardaway and associates demonstrated the development of pulmonary thrombi with associated shock in dogs subjected to the injection of incompatible blood. The pathologic findings in these dogs have a striking resemblance to those in our patient. The appearance of fibrinolysins has been reported after pulmonary operation.

I doubt that the fat embolization contributed much to the clinical picture. The fat may have arisen from the sternum which was split by the surgical incision. An alternative is suggested by the recent work of LeQuire and associates[13] who propose that aggregation of blood lipids is responsible for much of the fat seen in fat embolism. It is possible that plasma emulsifiers may have been altered concomitantly with alterations in the elements responsible for the coagulation of blood. Although the latter possibility is pure speculation, it seems unlikely that there is a sufficient amount of fat in the sternum



Fig 10 Photomicrograph of kidney showing scattered dilated and empty glomerular capillary loops A fat stain revealed the dilated loops to be filled with fat

to produce the emboli present at the time of autopsy

DR REED *Pathological diagnoses* (1) Subvalvular aortic stenosis possibly congenital (2) Rheumatic myocarditis mitral stenosis and aortic stenosis (3) Multiple widespread pulmonary thrombosis (4) Fat embolism in kidney and lung (5) Postoperative status thoracotomy aortotomy and aortic valvulotomy

Closing comments

DR LOVE It is *interesting to speculate* what role the active myocarditis could have had in causing the exercise intolerance We do know that many people carry a very high load of cardiac work for many many *years and have difficulty only* when some new event occurs such as the development of coronary insufficiency or myocarditis

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Annotations

The electrocardiogram in atrial septal defects and atrioventricular cushion defects

The electrocardiogram has proved to be of considerable value in the differentiation of atrial septal defect (ASD) of the ostium secundum type from those of the ostium primum type. Several recent excellent articles attest to this, although some observers have failed to confirm this differential diagnostic value of the electrocardiogram.

Atrial septal defects of the ostium secundum type may be subdivided into three types: (a) sinus venosus (persistent sinus venosus) (b) fossa ovalis (central) and (c) inferior caval. It is not possible to distinguish between these subtypes electrocardiographically. Ostium primum defects occur in the lower portion of the atrial septum in the region of the atrioventricular (A-V) valves and are usually associated with a cleft in the anterior leaflet of the mitral and occasionally in the septal leaflet of the tricuspid valve. This type has also been called the partial form of persistent common A-V canal. In the complete type of persistent common A-V canal, in addition to the ostium primum type of defect in the atrial septum, there is a ventricular septal defect (VSD) and a common A-V valve or fusion of the mitral and tricuspid valves across the top of the ventricular septum with small communication beneath.[19] The terms "endocardial cushion defect" or "A-V cushion defect" have also been applied to both partial and complete common A-V canal. Complete absence of the atrial septum is termed "common atrium" or "single auricle."[20]

The electrocardiogram in ASD of the ostium secundum type characteristically displays an rSR' in the right precordial leads (V_1–V_{3R}) and right axis deviation (RAD) in the standard leads. This rSR' pattern (QRS < 0.12 second) has been found to occur in about 65 per cent of the cases of ASD of the ostium secundum type.[2] The pattern of complete right bundle branch block (CRBBB) has been encountered in from 5 to 40 per cent of the cases.[2,3,4] Other patterns which may occur in the right precordial leads include qR, rR', Rs, rSr' (normal crista supraventricularis pattern) and rS.[26] The mean QRS axis in most cases lies between +60 and −150 degrees, with the majority lying between +90 and +150 degrees.[2,4,5,6]

The rSR' pattern (QRS < 0.1 second) in the right precordial lead in ASD has been variously termed incomplete right bundle branch block,[13,14] diastolic overload of the right ventricle,[15] and right ventricular outflow tract hypertrophy.

Cardiac catheterization studies in ASD have demonstrated that there is no delay in the onset of right ventricular systole such as would occur if there were true right bundle branch block.[17] Many of the recent studies favor dilatation and/or hypertrophy of the crista supraventricularis region of the right ventricle as the explanation for this pattern.[2,17,18]

The rSR' pattern is usually associated with normal or slightly elevated right ventricular and pulmonary arterial pressures.[2] If pulmonary hypertension supervenes and concentric right ventricular hypertrophy develops, the right precordial leads often display a qR or Rs configuration.[16,2,17,18] The occurrence of a qR or Rs pattern might also suggest the presence of some associated anomaly such as pulmonic stenosis or even mitral stenosis.[6]

The electrocardiographic pattern which has been found to be nearly pathognomonic of A-V cushion defects is left axis deviation (LAD) in the standard leads with the rSR' pattern in the right precordial leads. The LAD of the early QRS forces is usually in the range of 0 to −60 degrees,[19] whereas the mean QRS axis usually ranges from −60 to −180 degrees.[20]

Some workers have attributed the LAD to left ventricular enlargement secondary to the mitral insufficiency,[20,21] whereas others have favored a parietal wall conduction defect[22] or a congenital aberration of the left bundle branch system.[23] Burchell, DuShane and Brandenburg[4] have presented a critical review and rather convincing evidence in favor of the latter explanation.

The distinctive electrocardiographic pattern of LAD has been described in 80 to 100 per cent of A-V cushion defects.[19,4,17,20] Other workers, however, have not found such a high incidence of LAD and have even encountered right axis deviation (RAD) in some cases.[23] Burchell and associates have encountered some cases of partial or incomplete form *of A-V cushion defects without the typical electrocardiographic pattern, but no cases of the complete form without the characteristic electrocardiogram.*

In A-V cushion defect the right precordial leads may also display complete right bundle branch block or qR, R', rSr' or rS patterns which are not *diagnostically different from those of ASD of the* ostium secundum type. In the presence of mitral insufficiency the left precordial leads may or may not demonstrate left ventricular overloading or hypertrophy. Atrioventricular cushion defects [illegible]

been found to manifest q waves in left precordial leads twice as commonly (70 per cent) as do atrial septal defects of the ostium secundum type (35 per cent).[9]

The QRS vector loop in ASD of the ostium secundum type rotates clockwise in the frontal plane and is oriented below the isoelectric line (0 to 180 degrees) to the right and anteriorly.[3-8, 12] The QRS vector loop in A-V cushion defects rotates counterclockwise in the frontal plane and is oriented superior to the isoelectric line (0 to 180 degrees) to the left and posteriorly.[3-8, 10] A horizontal figure-of-eight pattern oriented along the isoelectric line with the initial part of the loop rotating counterclockwise also has been described in A-V cushion defects.[3, 4-8]

The ventricular gradient (G) in ostium secundum defects tends to be vertical and oriented to the left of the mean QRS ($\hat{A}_{QRS}$) whereas in A-V cushion defects G is horizontal and to the right of $\hat{A}_{QRS}$.

Prolongation of the P-R interval occurs more commonly in A-V cushion defect than in ostium secundum defects.[3-6] Atrial fibrillation has been described in about 10 per cent of the cases of ASD,[8, 12] being uncommon in the young but more frequent in older persons.[12] Atrial fibrillation is likewise uncommon in A-V cushion defects.[8] Tall P waves in Leads II, III, and aV are surprisingly infrequent,[3, 5, 14] although diphasic P waves in Lead V (V$_1$) which suggest right atrial enlargement has been described in about 50 per cent of the cases of both ASD and A-V cushion defect.[3-8]

In patients with common atrium LAD and counterclockwise rotation of the QRS loop identical to that in A-V cushion defects have been encountered. Another interesting feature noted by Keith[5] in cases of common atrium has been a P wave axis of −60 degrees together with a short P-R interval.

It is worth emphasizing that ASD of the ostium secundum type may occur with a normal precordial electrocardiogram (without the rSR pattern) with a normal axis and rarely with LAD.[3-5] The frontal vector may also occasionally be oriented superiorly above the isoelectric line or horizontally in a figure-of-eight pattern and have counterclockwise rotation.[8] Of considerable interest has been the observation that ostium secundum defects with acquired mitral insufficiency do not display LAD but may show RAD and clockwise rotation of the frontal vector.[4, 5]

Atrioventricular cushion defects occasionally may display a normal QRS axis and rarely even has RAD and clockwise rotation of the frontal vector loop.

Patients with pulmonic stenosis, patent ductus arteriosus, ventricular septal defect, or total anomalous venous return present occasionally an electrocardiographic pattern which resembles that characteristically found in ASD of the ostium secundum type.[3, 12]

Other types of congenital heart disease that may occasionally simulate the electrocardiographic pattern described in A-V cushion defects include (1) VSD especially those located posteriorly beneath the septal tricuspid leaflet, (2) combined ostium secundum defect and VSD,[8] (3) origin of both the aorta and pulmonary artery from the right ventricle,[13] (4) persistent truncus arteriosus,[13] (5) single ventricle,[1] (6) endocardial fibroelastosis.

Cases of tricuspid atresia display LAD but the initial forces, although horizontal, are not so leftward as in A-V cushion defect, and the right precordial leads do not exhibit the rSR pattern.

In conclusion, it appears that although there are significant exceptions, the electrocardiogram usually will permit a distinction to be made between ostium secundum and A-V cushion defect.

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Acute angioneurotic edema of the mitral valve

Contemp ary literature barren of feren t thi part l odin me F en Lunad m Ca d set ha nothin on th topic Althou h rare th con lit on does exi t nd t salient fea tures re orth discu in Dr F Tici d en sed ease hen I hi esident t the Cook Cou t (Chicago Ill Hosp d l ha been search for them nce nd in th report I present my third case

The ng lad in question as 3 ear-old medical tu lent She married nd h no children Since inf ncy he ha been unde tant careful med al opers ion beca se f rious food allergic nd thma H f mil ph icia thought he had n ttack of rheumat fever hen he 6 ears ol l H went her t Ariz here he pent sev ral ar t al ard g h l N d t er recorded cardiac murm ther ev l nc of card ac pathology

Since her return t N York he ha been rela tivel free f symptom l t ha er tinued under cl se medical observat l 19 8 before entering medical school he underwent battery of exha t e test Since everythi er lered t be ormal he wa permitted t u lert ke the pro p sed course Besides infreque t tri ial upper respirat ry infect n the l l h t l well Her la t ph ical check p n the ummer f 1960

On Tha k gi ing D of 1960 the patient woke p th light old but thi did not prevent her fr m preparing the u u l Thank gi ing meal After h ng the d hes nd le ning up he felt tire l and so ent t bed horth af er 8 r m However the sense of f tigue became progres ively orse nd he became r co scious of pounding rapid heart beat At 9 r m hen I sa her she as tting p n bed badl frightened nd fighting t catch her breath The pulse w 106 en nd full oral temperat re 98°F the blood pressure 94 6 mm Hg the l ng re till dry nd clea th excellent expa The he rt presented an amazin l forceful diast lic murmur with pre tol accentuatio Iso n m xtmal syst l mur mur heard the peral pulsatio marked nd a diastolic thrill f lt

Because of the pos Knowledge f the l sence of all nter lent card is patholo ies acut edema f the mitral l diagnosed In the expecta tion of pid lsadence f symp ms he rea ured m xmall g en a sedat hypnotic capsule l alcoh l c enge drink She rel xed l fell lep l d l t ll the husband to call me immediately if her symp t ms took turn for the orse I mad rl th t rnd l mea ures p t merg ncy cardiac op rat d l become imper ti if l sur f the mitral l threatene l

I the m rning the p tient entirel ecmf rt

able nd compo-ed There was ery marked diminution in the inten ity of the murmur The ECG howed only some l w in er ion The complet blood count w rmal except for 5 pe cent eosinophilia No further medication w deemed necessary although bed rest wa enforced After another da all ph al bnormalities were gone the heart sound h l re erted t complet rmalit The following w ek the tudent health center conducted searching test includ ng barium allow in the oblique position fluoroscopy blood tests ECG et E erything checked out entirely normal

Three month la er her h band devel ped ery severe upper respiratory infect on Tw days later the patient called me t say that she w beginning t feel again he had on the previou occasion Although thi ttack w not nearl so intense as the fir t one the double murmur in the mitral area was clearly udible again Thi time the patient received a 4 mg tablet of Chl Trimeton in addition to the sedation Within 2 hours the murmurs ere gone completely no epinephrine as needed She has been w ll since

Comment Obviousl hist logic sections ould be needed t actually *prove* the presence f the acute edema However the rapid fluctuation in the rmu quite characteri tic It eas t exclude such entities ball thrombu on either ide of the heart Tumors of the endocardium beha in their ow definite way There no infection that can gi thi rapid alternation of signs Acute allergic Fied ler myocarditi ca come on with startling rapidit but ha its ow quite different course The treat ment th antihistaminics sedation nd rest ha been quit adequate in the three ca es within my experience Use of epinephrine and oral ephedrine ould be logical

A fairly caref l search of the literature reveal ingle reference[6] to mitral valvulotomy for an edematous mit al structure I thi instance the French surgeon had 33 year-old oman who had had chorea t the of 13 Her ordinary clinical picture as that of mild mitral in fficiency Yet he was subject t repeated crises of par xysmal tachycardia pulmonary edema nocturnal hemoptys and even period of unconsciousness The t tending physicians concluded that the mild mitral tenosis w be ng aggra ted by periodic bout of edematous swelling of the al which would then become hut tight lmost compl tel On April 1951 the surgeon d l finger f acture of the tenotic ah Du souffle tolique di parait was paral leled by a excelle t clinical recovery

Ordma deal w th urticaria in con iderable det il but does not mention cardiac al ul r dise se Also thi ry article by Tragg entitled Hereditary Angioneurotic Edema h 34 references but again nothing i said about the mitral lve E thel gi t do not seem t ha described th ent t even though logic ould seem t require th t some in tances of acut edema of the cardiac valves as described abov mu t end lethally I it pos ible th t the condition goes unrecognized on the topsy tal le

It hoped that the present linical not ma again draw attention to the fact that epinephrine ca pos ibl be lifesaving when gi en in time Also t times emergency cardiac operation could be of tremendous alue—aga when done in time Acut edema of the mitral al will begin to be diagnosed again when thi ndrome recalled from limbo t general recognition

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Pulmonary artery dilatation as a cause of chest pain

The article by R S Ros on Right Ventricular H pertens on as Cause of Precordial Pain pub l hed in the January 1961 ue of the *American Heart Journal* provide further evidence hat the chest pain in pulmonary en ous l pulmonary hypertension the resul of righ entricular myocardial ischemia secondary t reduced coronary blood fl w wh h explained on the basis of elevated right entricular intraca itary pressures during both systole and dia tole

I 1953 w reported chest pain in 3 cases of congenital heart disease with d latat on of the pulmonary artery The diagnoses in these c were (1) pulmonary tenosis with atrial

defect (2) trial septal defect and (3) idiopathic pulmonary artery dilatation It was then already stressed that chest pain may occur without pulmonary hypertension It as ho pointed out that the disproportion bet en coronary blood flow and right entricular ork may explain the chest pa n onl in the patie t w th pulmonary stenosis It may however be contributing factor in the second patient th trial septal defect and diastolic overlo d f the ri ht entricle But this mechanism an ertainly not be held re ponsible for the chest pai bserved in the patient th idiopathic pulmon ry artery dilatation in whom right entricular nd pulmonary arterial pressures wer shown to be ompletely normal Since then we ha observed 6 additional patient w th idiopathic pulmonary artery dil t tion all ca es ere proved by cardiac catheterization The right ventricular systolic and diastolic pressu es as well as the pulmonary arterial pres ures were normal and there were no significant hanges in the oxygen content of the blood in the right side of the heart I 5 of these patients chest pain was a prominent feature The pain was sometimes brought bout by ph sical exertion but also occurred t rest The pa lasted from few minutes to sev ral hours It was frequently associated with dyspnea but was not relieved by nitroglycerin The exercise test (Master) was negative

Since the common denominator in the cases which e previously reported[2] and in the other 5 patients with idiopathic dilatation of the pulmonary artery is dilatation of the pulmonary artery the possibility has to be considered that the chest pain may be elicited by distention of the walls of the pulmonary artery even when pulmonary arterial pressure and right ventricular pressure are not elevated Possible afferent pathways from the pulmon ry artery are indicated by Viar and Harrison

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A letter from Sir James Mackenzie to Sir Thomas Lewis*

An intimat account of the lif of Sir James Mackenzie has been given by his friend nd pupil R McNair Wilson in his book so aptly titled *The Beloved Physician* The letter here reproduced presented by Sir Thomas Lewis to the l te Dr William P St Lawrence a Fellow of th Academy (New York Academy of Medicine) refers briefly to several matters with which the name of the write is closely associated It also reflect the informality of the relationship hich existed between t men who ha e exerted profound influence on the direction of thought in the field of cardiology

It was Mackenzie who fir t described tri l fibrillation in his book *The Study of the Pulse* in 190 At this time he referred t t as paral si of the auricles Only some ears later after dev ing the ink polygraph and nalyzing tracings from patient did he recognize the true nature of the cond tion The subsequent tudies of Lewis made with the aid of the electrocardiograph defined nd clarified the mechani m of fibrillation

Mackenzie alw y insisted on the importance of symptoms nd of accurat bedside observation T carry out his ideas in 1918 t the age of 65 he ga up his Harley Street practice and moved to St Andrew in Scotland there to establish one yea later The Inst tute for Clinical Research which now bears his name Not long after he had made this mov nginal pains first noted some years pre iously became more pronounced nd he died of acute myocardi l infarction at the age of 7 I the meantime in 1923 he h d publ hed his e d u ed olume *Angina Pectoris*

I the book *The Fut re of Medic ne* referred t in the letter Mackenzie expounded his view on this nd other related subjects There ere numerou critics of his doctrine yet these like his many friend loved and admired him To the end he belittled the use of mechanical devices nd continued to stress the fundamental importance of clinical research Late in lif he once remarked to Wilson with a smile If I had never in ented the ink polygraph I might never hav obt ined a hearing at all.

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New York N Y

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New Park St Andrews
Dec 4/18

Dear Lewis

I suppose you agree that the course I pprove in nearly every instance timulation of the respiratory centre & the chief source f timula tion is a deficient blood upply. The nature of the actual timulant deficient O exces e CO_2 in lactic or other acid. This latter problem I do not attempt to deal with as all the conflicting theories & experiments are beyond my comprehen ion.

I your argument if I understand you aright in say if there is no cyanosis therefore the breathless ne s is not cardiac in origin. I see we are at cros purposes. If a man with complete heart block goes rapidly up hill he becomes breathless. My explanation that the heart does not increase it output its rate unin fluenced. The demand for an exces upply to the muscles of the leg diminishes the amount to the respiratory centre & so causes breathlessness —without cyanosis. Rarely uch patient in place of being breathless are uncertain feel as if they would fall or the feet feel very he vy— here I take it of defi ient supply of blood to brain & legs. Many cases of auri fibrillation are cyanotic & very breathless some are breathless & not cyanotic. E en in cases of Cheyne-Stokes due to auri-fibrillation there is little cyanosis (I think sometimes none) but on digitalis lowering the rate the Cheyne Stokes disappear.

Henry James for year or 2 was pulled up every 200 yards by pain then he developed auri fibrillation & wa pulled up every 100 yard by breathlessness & no cyanosis.

I heard from Christian that he had written you for an article on mechanical aid in diag nosis of circulatory troubles. It tackled me for in my article I intend to demo stra e that the use of mechanical devices in the routine observation in practice is indicative of lack of kill in the physician & evidence that he ha not pa sed out of the Chrysalis stage. I ha e just fi ished once over the book I ha been engaged on—The F ture of Medicine—& I hope it will cause some searching of heart & I deal ery faithfully w th laboratory method.

I paid a vi t to MacWilliam a few day go & he has some ery pretty tuff on fibrillation. M tthew Hay dined w th u & he is one of the Carnegie tru tees w th 2½ millions t their disposal. He told me if I liked I ould ha any amount of money for my new research institut. I told him I was afraid it might prove failure & I would rather not ha the disgrace of getting money & not show a u ef l result. He was good enou h to say that they would not hesitat giv me the money to me even w th uch a prospect. And here ha e I made myself bond la to an American publ her quite unnecessarily particularly as the research will not be failure. Already it is panning out far better than I dared expect & once w get the thing going I am now confident that the lines I intend to follow will be fruitful. At present I can t get the apparatus nor the tant al thou h I hav partially engaged 2 or 3. M hands too are rather full with the F ture of Medicine & I ha e next to write a treatise for the confounded American. After that I hope to have the as tant & go full team ahead.

W thorou hly enjoy this place & the days flee pa t. I woul I stron l ad ise you t (put) down tool every now & again & flee w y & laze about & think real downright hard think ing. It is urpris ng how different my problems look nce I came here & I feel like the eagle when youth was renewed. The local guidebook tells of decrepit men of 70 coming here to die & they buck up & lead enjoyable lives till they get to 90. And here am I beginning new port —curling—& hooting like school bo y.

With best regards to Mrs. Lewis

Believe me yrs er t
J Mackenzie

Book reviews

ARTERIOSKLEROSE ... PATHOLOGIE KLINIK ... Dr Gotthard Schettler ... Medizinischen Klinik Stuttgart Bad ... Professor der ... tion with Prof Dr H B ... Dr H Hrdinger Tubi ... Dr J Lindner Hamburg ... Dr H Sautter ... Dr W Schulte Tubingen ... 1961 Georg Thieme Verlag 28 pages ... the U S A and Canada by ... Med ... Book Corp New York Inc $ 4 50

I ... Golden Age of cur ... med ... ne and ... the problem of arteriosclerosis ha ... med overwhelm ... again ... Although the ... quantity and the ingenuity of the in ... ork devoted t ... t measure up ... are till facing ... painful disproportion between magnitude of effort and con ... results Under such frustrating conditi ... undertaking of the auth ... himself experienced ... tor t ... present the entire problem complex of arteriosclerosis ... one ... competent co ... who ... tributed some ... pecial ... The first half of the book deal with the ... quest ... morphology chemistry ... the ... tat ... al ... h ... ject ... nd ... bem ... h ... sev ... bered ... how ... t ... fkt ... ps ... b ... ma ... res ... bem ... nam ... t ... es Hood ... nd diet Th ... m ... faceted m ... terial ... suburb ... al La bion and ha ... exten ... refere ... th ... Americ ... lte ature Th ... ha nost ... limitation ... lipoprote ... and serum ... holester ... lues are pr ... ted ... The establi hed import ... ce of dietary fa ... tak ... and of the balance between saturated ... saturated as ... recognized ... t ... t ... thout warning aga ... t ... rbitrary ... nd ... neurotic ... l dietary fad

It ... fascinatin ... to ... o ... par the ... ontent ... f Schettler book with earlier review ... on arteriosclerosis e g Cowdry ... olume ... hich wa publi ... hed in 1933 and to notice the ... hift ... empha ... from morphology to histochemistry ... ed from individual observation t ... epidemiological ... ta ... t ... tics

The second ... linical half ... f the b ... k gives ... nd p ... ture of the progress ... hich h ... been made ... d agnostic procedures and of the ... per ... taci ... ad ... ances ... vascular ... rgery Cli ... ical manifestations of arteriosclerosis in ... ll sections of the ... ascular tree ... re discussed in detail Illustrated by interesting case histories ... omple ... mented ... pecial ... hapters on ps ... hiatric and ad ... ert ... th ... therapy the use ... f hormones ... of drugs ... hich influence l ... pid metal ... ed ... prepared dietary tables for the Germ ... hold ... the conclu ... ch ... ter

Having in mind the regr ... tal le ... t ... mental separation of interests of most basic investigators on the one hand and of clinical research orkers ... nd practicing physicians on the other this reviewer wonder ... whether the book will prov ... equall ... useful to all of its readers However th ... ma ... be the fact remains that we ha ... here ... monumental achievement of unquestionable ... lue ... a guide to serious students of the problem of arteriosclerosis in its many manifestation The style ... fluent ... nd less ponderous ... nd involved tha ... much of the Germa ... scientific postwar ... riting The illustrations are beautiful if not la ... h Altogether Schettler book is unparalleled in present-da ... literature on the subject of arteriosclerosis

In order not to neglect his obligation of fa ... finding this reviewer ... ould like to mention from his own point of ... iew that in the discussion of coronary heart disease ... nd angina pectoris ... the differentiation between the ... sentially ... ascular ... nd the essentially myocardial phenomena ... ed might ha ... been desirable

This book ... an be heartil ... recommended to all those wh ... ar ... intere ted ... n or who should be ... ested ... rteriosclerosis

V ... R C ... E VEI ... A PRACTICAL MANUAL By R R wden Foote London With the assistance of A G ... don Dingley M A M Chir (C ntab) F R C S Con ultant Surgeon to the Southend-on Sea Group of Hospital Late Surgical Chief Assistant ... t St Bartholomew Hospital London Third edition Bri tol 1960 John Wright and Sons Ltd Excl ... ive U S agents William & Wilkins Co B ltimore Md 356 pages Price $13

Th ... book on ... eru ... is now ... ts third edi ... tion ... hich ... ttests to ... ide accept ... nce It deal comprehen ... ely ... th ... ll ... pects of ... ricose ... e ... nd rel ... ted problems The book is written ... informal readable style It is exceptionally ell ill ... ted ... nd thoroughl ... notated The uthor ha ... accompl ... hed his purpose of providing a ... Practical M ... nual ... on the management of aricose ... and the book is highly recommended to phy ... icians ... nd surgeons ... h ... de ... with these problems

ESSENTIAL HYPERTE ... SION An I ... ternat ... al Symposium Berne J ... ne 7 10 1960 ... ponsored by CIBA ... nder the chairma ... h p of F C Reid Ed ted by K D Bock ... nd P T Cottier Berlin 1960 Springer Verla 39 pages 81 ill ... tr tion Price DM 33 80 ... Il ... hed in ... n Engl ... h edition ... lso

Th ... nternational ... mpo ... um c ... ncerned ... th essential hyperten ... ha ... bee ... carried on in the fine t ... d ... tion ... f other CIBA symposia ... con ... tutes ... n ... thoritativ ... review of the ... ubject by ... di tinguished internati ... nal group ... f ... est ... gator The ... ject ... ers ... ell ... ered in ... ma ... l ... tions The book c ... t ... ut ... g ... d general ... eview of the f ... ld of essential hypertension

includes discu sion f tiology an l especiall therapy Pathology of the d sease discu sed only incidentally

The informed reade will find ery little th t i new this olume He will find however discu sion of most of the importa t development during the last 10 to 20 year w th references to a large mount of investigation during th period of time Much controver ial material i presented nd in this light the free uncure discus ion are particularl aluable in ma opinions are expres ed

The book is recommended a a general out line of accomplishments in the field of research and therapy of essential hypertension in recent year nd as a source of literature from which additional reading may be done

Hypokinetic Disease By Hans Kraus M D Associate Professor of Physical Medicine nd Rehabilitation New York U iver ty New York and Wilhelm Raab M D F A C P F A C C F C C P F A C S M Verm Emeritus Professor of Experimental Medicine and Director of the Cardiovascular Research Unit University of Vermont College of Medicine and Attending Physician DeGoesbriand Memorial H pital Burlington Vt With a foreword by Dr P ul D Wh t Springfield Ill 1961 Charles C Thomas Publisher 193 pages Price $7 50

Thi an interesting and challenging book Its major thesi the harmful effects of the modern sedentary lif particularly in the United States The first portion deal ith orthopedic disord rs and especially with the alue of physical exercise as method of treatment

The second part of the book concerned th cardiovascula disorders and includes a comprehen ive and scholarly review of the phy iologic clinical and stati tical literature The last portion concerns the relationship between lack of phy ical conditioning and emotional instability

Numerous charts and diagrams some of them of humorous nature as ell as tables clarif the text

The authors emphasize that the so-called athlete heart is abnormal only in the ense that it is supernormal Actually they con ider the thlete heart to be the normal heart nd the heart of sedentary individual to be functionally abnormal They emphasize repeatedly that these are not fixed *differences* but may be ltered in either direction by prolonged rest or by periods of training

A reviewer bo hed to emphasize the praiseworthy qualities h ch seem t be rare many reviewers ca find umber of minor fla For instance one questions he data quoted on page 68 which ind cate an erage card ac output of 2 l liters per m ute for the trained individual as compared w h 5 5 liters for the untrained Similarly there perhaps an ex cess n emphasis on the rol of adrenergic b tances in the etiology nd path genesis of the d fference between the heart of untrained and trained subjects Many reader will regard th emph interesting but based on theoretical rather th proved concept

These are m nor defect Act lly the ev dence a sembled from ide ariety of sources nd clearly presented almost overwhelming in indicating the importance of ph sical exercise a a means of achieving positi e he lth in the norm l population nd a means of reducing the lik lihood of coronary and other degenerative di eases in the older age groups

The extensi bibliography lone ould mak the book worth wh le for the laboratory or clinical in estigator ell f the practicing ph ician The arion hypotheses dvanced by the a thors are supported b con iderable body of ev dence and are both challenging nd tim lating

Flow Properties of Blood and Other Biological Systems Edited by A L Copley nd G Stainsby Proceedings of nformal discussion convened jointl by the Faraday Society (Colloid nd Biophysics Committee) nd the Brit h Society of Rheology held t the University Laboratory of Ph siology Oxford Sept 3 and 24 1959 New York 1960 Pergamon Pres 446 pages Price $1 50

A joint meeting under the ponsor hip of the Briti h Society of Rheology and committe of the F raday Society as held n Oxford England September 1959 to discu pects of the current st tu of Biorheolog the tudy of flow nd deformation in biologic material This olume contain the contribution presented by 48 uthors as w ll the informal discussion of ach of these papers These re grouped int h section (1) general lecture on the rheological properties of concentrated polymer solution (2) eleven paper dealing th Hemorheology (3) ten papers relating to tems other than blood (4) hort d scus ions of ten exhibits of pecialized pparatus nd (5) brief descriptu n related t seven sc entific films

Thi book follow the recent tre d of pub l hers to g impres nd somewhat mi lead ng title to reports of pecialized conferences of thi t pe This ork not necessarily sy tematic description of the present status of knowledge of the flow p operties of blood how ever does pro ide an introduction t major areas of act ty in thi field The participants th conference included phy iologi ts hema ologi ts phy i ians surgeon phy ici t chem ts mathematicians nd engineers The papers re highly technical and deal with the rheological properties of substance anging from hot chocolate and dead fi h to cervical mucus lymph nd blood This report will be useful to those who w h to make quick survey of activity in thi expanding field of investigation It will be of ery limited interest t the great majority of clinical cardiologi ts or to those investigators hose m jor interest does not touch on area

Announcements

The American College of Cardiology deadline for the YOUNG INVESTIGATORS AWARD for 1962 is January 1 1962 according to announcement by Gabriel F Greco M D Ozone Park N Y Chairman Public Relations Committee

The award is represented by a silver medal and $1 000 There will be one honorable mention award and $ 50 and eight additional awards of $100 each

Any physician in residence or fellowship status or within 3 years following this residence or fellowship is eligible to participate with a formal presentation 10 minutes in length describing original investigation placed in competition before the Eleventh Annual Meeting of the American College of Cardiology in Denver Colo May 29 to June 2 1962 An original manuscript and letter indicating intention to enter competition must be accompanied by letter from the chief of the service or laboratory indicating his willingness to have the material placed in the competition

Address queries and manuscripts to Executive Director American College of Cardiology Empire State Bldg 350 Fifth Ave New York 1 N Y

Reprints are available for the CONFERENCE ON MECHANISM OF EXPERIMENTAL RENAL HYPERTENSION held in August Mich April 22 and 23 1961 with Dr S W Hoobler Ann Arbor Mich Chairman and Dr A C Corcoran Cleveland Ohio as Vice Chairman

The program was as follows *Review of Physiologic Mechanisms* Renin—Dr P Blaquier Ann Arbor Mich Liver—Dr H F Loyke Cleveland Ohio Adrenal—Dr P Rondell Ann Arbor Mich Kidney—C Wilson London England *Review of Vessel Wall Changes* Reactivity of Arterioles—Dr D F Bohr Ann Arbor Mich Arteriolar Rigidity—Dr J Conway Ann Arbor Mich Effect of Hypertension on Vessel Walls—Dr G M Wilson Cleveland Ohio *Review of Humoral Substances* Antihypertensive Substance From Kidney—Dr F M Sturtevant Detroit Mich Anephrotensin—Dr R Rosas Santiago Chile Angiotensin—Dr Skeggs Cleveland Ohio and Dr Boucher Montreal Canada Renin—Dr Helmer Indianapolis Ind

Abstracts of discussion by the following additional participants Dr L Beck Dr R Correa Mr John Schroeder M R Warzynski all of Ann Arbor Mich Dr F Bumpus and Dr F Haas of Cleveland Ohio Dr W Freyburger Kalamazoo Mich and Dr J Genest Montreal Canada

The reprint containing about 50 pages of original work and review may be obtained free of charge by written request to Dr Walter Freyburger Upjohn Company Kalamazoo Mich

The University of Texas Postgraduate School of Medicine is pleased to announce a SYMPOSIUM ON CARDIAC ARRHYTHMIAS scheduled for Dec 8 9 and 10 1961 The symposium will be held in the Texas Medical Center Houston Texas and the program will be presented by three outstanding guest lecturers augmented by local faculty The three guest lecturers are Dr Samuel Bellet of Philadelphia Dr David Scherf of New York City and Dr Paul Zoll of Boston

For further information write Office of the Dean The University of Texas Postgraduate School of Medicine 102 Jesse Jones Library Building Texas Medical Center Houston 25 Texas

The American College of Cardiology will hold WORKSHOP IN CARDIOLOGY at the Institute for Cardiopulmonary Diseases of the Scripps Clinic and Research Foundation in La Jolla Calif Dec 5 8 1961 according to an announcement by Gabriel F Greco M D Chairman Public Relations Committee E Grey Dimond M D President of the College will preside assisted by 24 instructors from the Institute

Coverage of recent developments in basic and clinic research will include principles and diagnostic value of electrocardiography vectorcardiography phonocardiography cineangiography indicator-dilution studies monitoring of cardiovascular events respiratory instrumentation congenital and acquired heart disease the biochemistry of myocardium and blood vessels with emphasis on relationships of the carbohydrates the cardiac glycosides the lipids and the catecholamines to clotting mechanisms disease There will be case presentations clinical pathologic sessions question and answer period panel discussions illustrated by a profuse number of tracings x-rays and laboratory findings

The program will run four full days from 9:00 A M to 5:00 P M daily and two evening sessions from 7:00 P M to 9:00 P M Tuition is $50 00 for members and fellows of the American College of Cardiology and $100 00 for other physicians Residents and internes will be admitted without charge Advance enrollment is required

For further information write Philip Reichert M D Executive Director American College of Cardiology Empire State Bldg New York 1 N Y

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Acknowledgment to reviewers

The Editors wish to express their thanks and appreciation to the following who have aided in the review of manuscripts during the past year.

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made to prevent circulatory collapse and to combat it vigorously once it has occurred

Although renal ischemia or nephrotoxins probably account for the majority of cases of intrinsic acute renal failure the fact remains that in about one third of the cases no single cause can be determined with assurance Nor do we know why one individual may suffer from severe oligemic shock with no subsequent renal damage whereas another person whose hypotension has been of minimal severity and duration develops renal failure

Once it has been ascertained that the urinary suppression cannot be cured by improving the circulation or removing an obstruction the problem then is that of combating the physiologic consequences of renal failure which result largely from the loss of two important renal functions the function of maintaining a relatively constant volume and electrolyte composition of the extracellular fluid and the function of removing certain products of catabolism which are no longer required by the body In acute renal failure these tasks devolve upon the physician The first of these presents no difficulty By assiduous *control* of what is allowed to enter the body the volume of the extracellular fluid may be maintained constant and its composition stable save for the accumulation of the products of catabolism The intake of water should equal the measured losses through all channels plus the difference between insensible loss and insensible gain The former for a 70 kilogram adult resting afebrile in a temperate environment is about 800 ml evaporated from skin and lungs The latter amounts to about 400 ml derived from catabolism and preformed cell water Thus the daily water requirement is the measured loss plus about 400 ml Since the estimate of insensible loss and gain is at best an approximation the most satisfactory guide of water balance is careful daily weighing of the patient A daily loss of 200 to 300 Gm (from the catabolism of body tissue) is indicative of a reasonably satisfactory fluid balance The severely oliguric or anuric patient will obviously lose no appreciable sodium in urine However extrarenal losses—emesis diarrhea drainage—should be replaced quantitatively

Since the end products of fat and carbohydrate metabolism consist chiefly of carbon dioxide and water in amounts readily disposed of by the lungs it is largely products of protein metabolism—sulfate phosphate hydrogen ion potassium magnesium and nitrogenous moieties—which accumulate during urinary suppression and which can be minimized by reducing protein catabolism to as low a level as possible Although acidosis is to be expected as a chemical finding in acute renal failure it seldom presents clinical manifestations Similarly the hypocalcemia which accompanies the rising levels of serum phosphate rarely leads to tetany nor does elevation of serum magnesium often present a clinical problem

The accumulation of potassium in the extracellular fluid however constitutes a real problem since fatal cardiac arrhythmias result from sufficient elevation of the concentration of potassium in the serum For readers of this Journal it is unnecessary to detail the sequence of electrocardiographic changes which ensue as the concentration of potassium in the extracellular fluid rises nor to emphasize that the electrocardiogram rather than the actual level of potassium serves as the best indicator of impending catastrophe

Of the nitrogenous moieties of protein catabolism urea constitutes the quantitatively largest fraction However there is little evidence that urea at the highest concentrations encountered clinically is directly responsible for any symptoms in man and in fact it is stated that patients show clinical improvement after dialyses against a urea content of the bath which is sufficiently high to prevent lowering of their blood urea concentration

Although urea itself appears to be nontoxic when its concentration in the serum rises there is a similar elevation in its concentration within the lumen of the gastrointestinal tract where there are enzymes capable of forming ammonia from urea A local irritant effect of this ammonia has been held responsible for the anorexia nausea and emesis which may be encountered in uremia and a systemic effect appears implicated in patients with azotemia and liver disease who apparently cannot readily reconvert ammonia formed

Editorial

Acute suppression of urine

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The term *urinary suppression* has an old fashioned ring. Today terms more indicative of scientific erudition have succeeded one another—hemoglobinuric nephrosis, lower nephron nephrosis, acute tubular necrosis, acute renal failure, and the like—regardless of whether they possess anatomic or physiologic validity. We have used the term *acute suppression of urine* as a title not only because scanty or no urine is the essence of our subject matter but also because this is the observed clinical phenomenon.

Urinary suppression does not imply renal disease. It can occur in the presence of entirely normal kidneys if the renal blood flow is sufficiently reduced or if the outflow of urine is obstructed. In either situation—inadequate inflow of blood or inadequate outflow of urine—prompt recognition and appropriate treatment not only cures the urinary suppression but prevents the renal damage which is so prone to follow prolonged renal ischemia or obstruction of the urinary tract.

Although circulatory collapse (shock) is the most common cause of renal ischemia, it must be remembered that the systemic arterial pressure need not be excessively low. Renal vasoconstriction may virtually deprive the kidneys of blood and yet, by diverting the usually large proportion of cardiac output from the kidneys, serve to sustain the circulation elsewhere.

Obstruction at the neck of the bladder or below is easily recognized. Not so, however, that which simultaneously, or more often successively, blocks first one and then the other ureter. Unless the cause of urinary suppression is crystal clear, ureteral catheterization to establish patency is obligatory.

The intrarenal causes of acute urinary suppression cannot be cured, for the most part, by the active intervention of the physician as can those causes due to impaired inflow or outflow. However, the majority of lesions are reversible if the patient can be kept alive and in a reasonable state of health for a long enough time. Since irreversibility is rarely predictable, a hopeful attitude is always in order.

Little is to be gained by listing the innumerable causes of intrinsic acute renal failure save to note that specific measures as well as general ones may be indicated. In acute poststreptococcal glomerulonephritis penicillin therapy may be in order. Although probably too late to be of much usefulness once urinary suppression from mercury poisoning has occurred, dimercaprol (BAL) should be employed. In pyelonephritis, and particularly that variety known as acute papillary necrosis, the offending organism must be isolated, appropriate antibacterial therapy instituted, and the precipitating urinary tract obstruction and/or diabetes treated. It is, of course, paramount that every endeavor be

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patients with milder and briefer episodes of urinary suppression were treated and recovered at the local level of hospitalization. Over the past 9 years during which approximately 18 000 major surgical operations have been performed in my hospital there has been only one case of acute tubular necrosis consequent to such operation in which the renal lesion was the important contributory cause of death—death on the seventh day due to pulmonary edema from fluid overloading

This is not intended to minimize the alarming mortality encountered among patients with severe post traumatic or postsurgical acute renal failure such as are admitted to specialized renal centers. This mortality is found despite rather free use of external dialysis employed to correct electrolyte abnormalities or clinical manifestations associated with the uremic state and appears to be associated with poor wound healing and sepsis. Teschan and his associates[4] particularly note that these complications are conspicuous in the patients who develop oliguric renal failure but relatively rare in patients subjected to similar surgical or accidental trauma who do not develop urinary suppression. They believe that these may not be complications at all but rather manifestations of the damaging influence of the uremic state on recuperative or homeostatic processes and physiologic defense mechanisms.

I cannot comment on the phenomenon of poor wound healing since I have not seen severe postsurgical or traumatic cases. In the nephrotoxic group I have not been impressed with any undue susceptibility to infection other than might be expected particularly where there has been instrumentation of the urinary tract. Furthermore I am not aware of an undue prevalence of infection in patients who are suffering from chronic uremia despite the fact that these individuals are anemic, often are undernourished because of anorexia and vomiting, frequently suffer from chronic acidosis and may exhibit a tendency to bleed. Nor am I aware of reports of undue susceptibility to infection. In a recent study of *terminal* pneumonia contributory to the death of the patient Freeland and Price[5] found ...

dence in renal disease than in malignancy, brain disease or congestive heart failure.

Nonetheless, the mortality in the post surgical and traumatic cases of severe oliguric renal failure is such that Teschan's suggestion of prophylactic dialysis to prevent the uremic state deserves careful consideration. Whether this procedure will be of value cannot be determined a priori on theoretical ground. Only a carefully controlled clinical appraisal will furnish the desired information. In the meantime dialytic treatment seems to be indicated for patients who fall in one of two groups.

The first group includes those whose level of serum potassium and electrocardiogram suggest that a serious arrhythmia is in the immediate offing. The indication for dialysis (in order to lower serum potassium) in this group seems absolute. Temporary measures such as the intravenous infusion of dextrose and insulin or the administration of sodium bicarbonate should be employed to lower serum potassium in situations in which a life threatening arrhythmia seems imminent only until some other means of eliminating potassium from the body can be readied.

However when time is not of the essence and cardiac catastrophe is not anticipated within hours there is now available a method of lowering serum potassium and of maintaining it at a normal level. Carboxylic cation-exchange resins capable of removing potassium from the gastrointestinal secretions have been available for a decade. However their large mesh size made them unpalatable in general and particularly for the uremic patient with a propensity for nausea and emesis. Furthermore, they tended to form conglomerate masses in the stool which often led to fecal impaction. A new sodium-exchange resin (Kayexalate, Winthrop Laboratories, New York City) has the consistence of a powder which can be suspended in a small volume of water and ingested without difficulty. It has a theoretical binding capacity of 3.1 milliequivalents per gram of resin and in practice, has been found to exchange about 1 milliequivalent of potassium per gram. Combined administration of 10 to 20 ml of ... cent sorbitol syrup every few

in the gastrointestinal tract to urea and who may develop confusion and coma associated with an elevated concentration of ammonia in the blood.[3] It should also be mentioned that the bacteria in the gastrointestinal tract are capable of forming free phenolic derivatives[4] from the aromatic amino acids—tyrosine, phenylalanine, and tryptophane—which may adversely affect the nervous system. Blood guanidine (and derivatives) become elevated in renal failure. In dogs injections of guanidine cause gastrointestinal disorders and muscular twitching. However, the amounts used experimentally were far above any ever encountered in terminal uremia in man. Although high concentrations of both creatinine and urate are encountered, there is no evidence that they lead to the production of symptoms. Other nitrogenous moieties which result from protein catabolism or gastrointestinal bacterial degradation of nitrogenous substances have not been sufficiently studied to warrant discussion.

The desired diminution in protein catabolism is accomplished in two ways: no exogenous protein is administered; endogenous catabolism is reduced by affording a constant supply of glucose and by maintaining complete rest. The regimen then for the management of the patient with uncomplicated acute renal failure is most simple: (1) complete rest, (2) water in an amount so that body weight decreases daily by about 200 or 300 grams, (3) dextrose in a minimal amount of 100 Gm. daily, given in divided doses throughout the 24 hours, (4) sodium given only to replace losses, (5) avoidance of any other intake and particular caution in the administration of medications including antibiotics which are usually eliminated in the urine and which may accumulate in the patient with oliguria.

With such a regimen the patient with *uncomplicated* renal failure rarely presents any but minor manifestations of uremia despite elevation of the serum nonprotein nitrogen to 200 to 300 mg./100 ml., and the onset of diuresis is seldom delayed beyond 10 days if the intrinsic renal lesion is due to a nephrotoxin. I have seen such cases due to ingestion of mercuric chloride, inhalation of carbon tetrachloride, sensitivity to sulfonamides, and the ingestion of unknown nephrotoxins. The mortality in such *uncomplicated* acute renal failure is virtually nil—but unfortunately the number of such *uncomplicated* cases is also small. The would-be suicide is prone to ingest sufficient mercuric chloride so that severe hemorrhagic enterocolitis results, and the victim of carbon tetrachloride has often ingested or inhaled an amount that destroys his liver long before urinary suppression becomes a limiting factor for his existence. By and large, acute renal failure occurs in the setting of antecedent disease, major surgical or accidental trauma, or combinations of these. Thus of 100 cases analyzed by Bluemle, Webster, and Elkinton[6] (75 of these patients were sent to the Hospital of the University of Pennsylvania after an average period of oliguria of 1 week) only 9 were due to nephrotoxins. Four of these cases were uncomplicated and the patients survived. Three of the deaths after inhalation of carbon tetrachloride were ascribed to hepatic necrosis, and the 2 deaths after mercury poisoning resulted from infection secondary to the gastrointestinal lesion rather than to the renal disorder. Of 38 cases which developed after operation or other trauma, death ensued in 28.

Similar data may be noted in the report of Shackman, Milne, and Struthers[7] of patients transferred to the Hammersmith Hospital in London for treatment of acute renal failure. Death occurred in 42 of 50 surgical cases and in 22 of 29 cases of post-traumatic oliguric renal failure.

Teschan and his associates of the Renal Branch of the U. S. Army Surgical Research Unit at Fort Sam Houston, Texas, report 160 fatalities in 242 post-traumatic cases (both surgical and accidental trauma are included) collected by the Study Group on Acute Renal Failure. The source of the patients is not given, but presumably many were transferred from local hospitals to renal centers.

Frightening as the above figures are, it must be borne in mind that they have been collected from renal units and for the most part represent referred cases, patients who were considered by the originating institution as likely to require specialized treatment. No doubt many

patients with milder and briefer episodes of urinary suppression were treated and recovered at the local level of hospitalization. Over the past 9 years, during which approximately 18,000 major surgical operations have been performed in my hospital, there has been only one case of acute tubular necrosis consequent to such operation in which the renal lesion was the important contributory cause of death—death on the seventh day due to pulmonary edema from fluid overloading.

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modest diarrhea was produced a dose of 15 Gm of the resin given four times daily was uniformly effective in causing a gradual lowering of the levels of serum potassium in a group of severely oliguric patients Rectal administration was also found to be effective Once the level of potassium in the serum became normal 5 Gm three or four times daily was sufficient to prevent subsequent elevation

The second group for whom dialytic treatment may be indicated includes patients who are doing poorly and have uremic symptoms It is worth stressing however that the signs and symptoms of uremia may be difficult to distinguish from those of anoxia hypercapnia sepsis or liver disease Merrill and others who have had a large experience with hemodialysis are fairly unanimous in the opinion that such treatment results in a generally improved status which may allow the patient to tolerate other complications more successfully However in the absence of properly controlled studies of morbidity and mortality with and without hemodialysis we cannot comment on the utility of the procedure save in cases of life endangering hyperkalemia

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Clinical communications

What is Fallot's tetralogy?

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The classic association of morbid anatomic features described by Fallot[1] in 1888 and usually accepted as constituting the tetralogy which bears his name comprise pulmonary stenosis or atresia, ventricular septal defect, overriding aorta and hypertrophy of the right ventricle. But there is a wide range of both morbid anatomy and symptomatology among patients whose hearts possess a ventricular septal defect and pulmonary stenosis and there is a difference of opinion about what constitutes Fallot's tetralogy. Furthermore the hemodynamic errors which result are imperfectly understood.

One point of confusion is whether or not the term *Fallot's tetralogy* implies that there is cyanosis or at least that there is arterial oxygen unsaturation. Patients are sometimes divided into those who are cyanotic and those who are not. I prefer that the term should be confined to patients who exhibit desaturation of the arterial blood despite the fact that progressive pulmonary stenosis may occur and may result in the development of cyanosis in a patient who was previously not cyanotic. It is best used to describe patients who have pulmonary stenosis and a ventricular septal defect with a right to left (reversed) shunt. The several features of Fallot's tetralogy will be discussed and an attempt will be made to define the condition and to relate it to certain other conditions.

Hypertrophy of the right ventricle. Hypertrophy of the right ventricle merely indicates that this chamber is subject to strain. It seems inexpedient to include this feature as part of the complex of anomalies which constitute Fallot's tetralogy. It is no more a part of the picture of this condition than it is of many others which impose a strain upon the right ventricle.

Dextroposition of the aorta. Dextroposition of the aorta with overriding of both ventricles is usually considered to be an essential feature of Fallot's tetralogy [illegible] and its degree is believed by many to be an important factor in determining the amount of cyanosis[4] by causing the aorta to receive some blood directly from the right ventricle [illegible]. Keith, Rowe and Vlad [illegible] however state that some of their most severely anoxic infants have had only moderate overriding of the aorta.

An examination of the evidence casts serious doubts on the importance of aortic override in producing hemodynamic errors in Fallot's tetralogy. The degree of override found is extremely variable[2] [illegible]; it may be absent in a few patients who otherwise appear to have typical tetralogy, and it may be present in patients who have a ventricular septal defect but no pulmonary stenosis as in the Eisenmenger complex. The anatomic studies of Selzer[4] and Selzer and Laqueur[4] have shown that whereas varying degrees of aortic override from inappreciable to major can occur in Fallot's tetralogy, the recognition of the milder degrees is difficult when there is a large defect of the membranous septum even on direct examination. All who ha-

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studied hearts at postmortem examination would agree with this observation. Dextroposition of the aorta is thus an unreliable index of Fallot's tetralogy.

There is good evidence to prove that overriding of the aorta is unimportant in the causation of cyanosis due to a right to left shunt. The relief of pulmonary stenosis by closed infundibular resection or pulmonary valvotomy by the technique of Brock may relieve cyanosis completely and convert the right to left interventricular shunt into one which is entirely from left to right, despite the fact that the aorta is still overriding. A similar condition follows the open repair of Fallot's tetralogy if the pulmonary stenosis is eliminated but the ventricular septal defect is imperfectly closed, and this may lead to death.

Additional evidence of the functional unimportance of dextroposition of the aorta is provided by cases of "atypical" Fallot's tetralogy. Rowe, Vlad, and Keith[15] report four such cases in which a ventricular septal defect combined with pulmonary stenosis was associated with a large left to right shunt, normal arterial oxygen saturation, and systemic systolic pressures in the right ventricle. Aortic override was thought to be present in all four of these patients. In three of them a catheter entered the aorta from the right ventricle, the right ventricular pressure pulses were of normal pattern in the two in whom they could be satisfactorily analyzed, the aorta arched to the right side in one of them, and in the one who came to autopsy (not the one with a right aortic arch) a considerable degree of aortic override was found. Keith, Rowe, and Vlad have added a fifth patient to these four, and this patient also had an aortic arch on the right side. An aortic arch on the right side is rarely associated with simple ventricular septal defect or pulmonary stenosis with normal aortic root. Keith[1] found only one example in 400 patients with ventricular septal defects and Campbell[16] found only one among 5 patients with simple pulmonary stenosis. Rowe, Vlad, and Keith[15] found no example of such an association among 100 patients.

The evidence, therefore, is that the degree of aortic override in Fallot's tetralogy is extremely variable, that its recognition, at least in the milder degrees, is not easy, and that it has little influence upon the direction of shunts or the severity of cyanosis. In this latter respect Fallot's tetralogy resembles Eisenmenger's complex. Eisenmenger[16] himself maintained that overriding of the aorta was of little functional importance in the complex which he described, and the evidence in favor of this much debated opinion has recently been ably marshaled by Wood.[17] Dextroposition may, however, have some embryologic significance, for it occurs in about 20 per cent of the cases of Fallot's tetralogy and in a similar proportion of cases of the Eisenmenger complex. It also occurs commonly in transposition of the great vessels and in persistent truncus arteriosus. These are all conditions associated with large ventricular septal defects of the nonrestrictive type (*vide infra*) and/or anomalous septation of the truncus arteriosus and bulbus cordis. Both Selzer[3] and Warden and associates,[18] however, point out that the override may be partly acquired after birth as the result of disproportionate flow of blood through the aorta and the pulmonary artery. Eisenmenger[16] demonstrated that the aorta is normally located in such a relation to the ventricular septum that if the membranous portion of the latter is deficient it comes in contact with both ventricles, so that overriding of the aorta is a by-product of a large ventricular septal defect and not a developmental dextroposition.

The ventricular septal defect. The combination of a ventricular septal defect of a critical size with pulmonary stenosis of a critical degree of severity is the essence of Fallot's tetralogy. The writer has classified interventricular and aortopulmonary communications into nonrestrictive and restrictive varieties and has given an account of the hemodynamic upsets to which they give rise.[9] A nonrestrictive defect is one which neither restricts the flow of blood nor occasions a pressure gradient. The resistance to flow through such a communication is not greater, and may be much less, than that afforded by the normal pathways. In the case of a ventricular septal defect this is so when the diameter

of the orifice equals or exceeds that of the aortic root,[illegible] but the definition is a hemodynamic and not an anatomic one. A restrictive defect is smaller than this so that it offers a higher resistance to flow than does the normal pathway, and it creates a pressure gradient between the chambers or vessels which it connects.

A nonrestrictive ventricular septal defect will insure that the pressure in the two ventricles will be identical throughout the cardiac cycle under all conditions. Furthermore, throughout the ejection phase the pressure in the aorta and pulmonary artery will be the same as that in the ventricles, provided that there is no obstruction to outflow from either ventricle. If pulmonary or aortic stenosis is present, the pressure in the vessel beyond the obstruction will of course fall. In Fallot's tetralogy the pressure in the two ventricles is, in fact, the same throughout the cardiac cycle and their systolic pressures are identical with that in the aorta,[illegible] because the ventricular septal defect is always of the nonrestrictive type. Additional proof of this reasoning is afforded by the fact that after relief of the pulmonary stenosis by infundibular resection or pulmonary valvotomy, the pressures in the two ventricles and in the aorta (during systole) remain identical even though relief of the stenosis is sufficient to cause a large left-to-right shunt with pulmonary flows two or more times greater than systemic flows, oxygen saturations in the arterial blood of 95 per cent or more, and pulmonary arterial systolic pressures of up to 60 mm. Hg.[illegible] These findings prove that in Fallot's tetralogy the equality of pressures in the two ventricles is due entirely to the nonrestrictive nature of the interventricular communication and is independent of the pulmonary stenosis.

In Fallot's tetralogy the ventricular septal defect is nonrestrictive functionally and large anatomically; it varies between 1 and 3 cm. in diameter.[illegible] In Eisenmenger's complex also the defect usually measures between 1 and 3 cm. in diameter,[illegible] whereas in uncomplicated ventricular septal defect it is more often less than 1 cm. across. Kirklin and associates define Fallot's tetralogy as a congenital cardiac malformation with ventricular septal defect of a size approximating the aortic orifice and pulmonary stenosis of such severity that it in combination with the ventricular septal defect results in identical right and left ventricular pressures. I would disagree with this definition in that I do not believe that the pulmonary stenosis plays any part in maintaining equality of pressures in the two ventricles.

Because the ventricular septal defect is nonrestrictive in Fallot's tetralogy, the pressure pulses recorded from the two ventricles are identical and of normal pattern with an ejection phase plateau. This distinguishes Fallot's tetralogy from pulmonary stenosis with normal aortic root, in which condition Bouchard and Cornu[illegible] have shown that there is a typical and abnormal right ventricular pressure pulse. This displays delayed ascent during isometric contraction, absence of the ejection phase plateau, and delayed fall in pressure resulting in a symmetrical pointed tracing which is strikingly different from the left ventricular tracing from the same patient. Rowe, Vlad and Keith[illegible] found the abnormal type of curve in two patients with simple pulmonary stenosis plus a ventricular septal defect, so that the combination of the two anomalies need not affect the characteristic curve found in simple pulmonary stenosis. In such cases the septal defect is small and restrictive.

The characteristic feature of the ventricular septal defect in Fallot's tetralogy, therefore, is that it is nonrestrictive and this ensures equality of pressure in the two ventricles at all times, under all conditions, and irrespective of the presence and degree of pulmonary stenosis.

Pulmonary stenosis. Pulmonary stenosis is as fundamental a feature of Fallot's tetralogy as is a nonrestrictive ventricular septal defect. The stenosis usually occurs in the infundibulum, where it may be high, intermediate or low,[11] but it may be at the pulmonary valve or affect both sites. Rarely it occurs in the pulmonary trunk;[illegible] the writer has seen one such case. Fallot classified pulmonary stenosis and atresia combined with dextroposition of the aorta as a single anomaly. Although pathologically atresia represents the ulti

mate in stenosis hemodynamically, it profoundly alters the course of the blood supply to the lungs,[9, 6] which is by way of the aorta and thence the bronchial arteries and the ductus arteriosus. The prognosis of this condition is much more grave, and it is better classified under a separate heading.

Although pulmonary stenosis (or atresia) plays no part in maintaining equality of pressure in the two ventricles, it does account for two important features of Fallot's tetralogy, namely, the right-to-left interventricular shunt and the reduced pressure and flow in the pulmonary artery and its branches.

The severity of the pulmonary stenosis is critical, for if the resistance which it imposes on the flow of blood exceeds the systemic vascular resistance, then the shunt between the ventricles will be from right to left, whereas if it is less than this the shunt will be in the opposite direction. When the two resistances are approximately the same, the shunt will be balanced or bidirectional.

A relative increase in severity of pulmonary stenosis with age may cause shunt reversal and so convert a patient who is not cyanotic into one who is cyanotic. It is easy to relate atypical cases of Fallot's tetralogy with clinical and physiologic shunts from left to right[7, 19] to the classic variety with cyanosis. It is simply a matter of whether the pulmonary stenosis offers more or less obstruction to flow than does the systemic peripheral vascular resistance.

Alterations in the balance between these two resistances readily explain the marked alterations in the degree of cyanosis which may occur rapidly in children with Fallot's tetralogy and the attacks of cyanosis to which they are liable, especially between the ages of 6 and 18 months. These may be caused either by a transient increase in the severity of stenosis or by a decrease in the systemic peripheral vascular resistance.

Hamilton, Winslow, and Hamilton[14] demonstrated a decrease in peripheral vascular resistance in one patient, and this mechanism forms a ready explanation of the relationship of attacks of cyanosis to hot weather and infections which was noted by Keith, Rowe, and Vlad[9 (p. 490)] but which they ascribed to loss of extracellular water with deleterious changes in the already abnormal ratio of cell volume to plasma. Wood[28] showed that the administration of amyl nitrite produced an increase of cyanosis and of arterial oxygen unsaturation with a fall in the mean and pulse pressure in the pulmonary artery which accompanied the fall in systemic blood pressure.

On the other hand, Wood[28] also demonstrated that in five patients with Fallot's tetralogy spontaneous attacks of cyanosis with or without syncope were caused by an increased resistance in the pulmonary outflow tract and that the blood pressure did not fall in any of these patients. Functional infundibular stenosis operates in this manner whether the organic stenosis is valvar or infundibular. When consciousness is lost, arterial oxygen unsaturation becomes extreme, the pulmonary arterial pressure becomes very low, the murmur disappears, and a state of functional pulmonary atresia is established.[28, 7]

Wood[28] believes that the spontaneous attacks of cyanosis which occur in Fallot's tetralogy are due to functional infundibular stenosis, which explains their relief by morphine or cyclopropane, and concluded with confidence that peripheral vasodilatation is not the cause of these attacks. This, however, is probably not invariably so, and it cannot explain attacks which occur in patients who have organic pulmonary atresia.

Definition of Fallot's tetralogy. From the foregoing analysis I conclude that the fundamental feature of cyanosis in Fallot's tetralogy is the combination of a nonrestrictive ventricular septal defect with pulmonary stenosis of such degree that it imposes a resistance to the flow of blood which is greater than that caused by the systemic peripheral vascular resistance. Overriding of a dextroposed aorta, although usually present, is of little importance hemodynamically, but it may have embryologic significance. Hypertrophy of the right ventricle should not be named as part of an abnormal developmental complex.

Fallot's tetralogy may conveniently be defined as pulmonary stenosis with re-

versed or bidirectional shunt through a nonrestrictive ventricular septal defect. The term *Fallot's tetralogy* is a misnomer for there are only three developmental defects and one of these is unimportant functionally and extremely variable in degree anatomically. If an eponymous title is still desirable to honor him who described the condition so well even though he was not the first to do so[29] and because of its brevity then the term *Fallot's anomaly* would be more appropriate.

The definition suggested above is functional rather than anatomic. It excludes patients with left to right shunts who are not cyanotic but allows that the only difference is in the severity of the pulmonary stenosis. There is a close analogy between the conditions discussed in this paper on the one hand and those characterized by interventricular or aortopulmonary communications without pulmonary stenosis on the other. When the pulmonary vascular resistance is low the shunt is from left to right but when it reaches and then exceeds the systemic vascular resistance the shunt becomes balanced or bidirectional and then reversed. Eisenmenger's syndrome results and if the shunt is an interventricular one the condition is called *Eisenmenger's complex*. The fundamental difference between Fallot's anomaly and Eisenmenger's complex is that in the former the obstruction to pulmonary flow is in the region of the pulmonary infundibulum or valve whereas in the latter it is in the region of the small pulmonary muscular arteries. The definition of Fallot's anomaly given here is in line with that suggested for Eisenmenger's complex by Wood namely pulmonary hypertension at systemic level due to a high pulmonary vascular resistance (over 800 dynes sec/cm) with reversed or bidirectional shunt through a large ventricular septal defect (1.5 to 3 cm across). Communications between the two circulations which produce the Eisenmenger reaction are nearly always of the non restrictive variety when they occur at the ventricular or aortopulmonary level.

Summary

The essence of Fallot's tetralogy is the combination of a nonrestrictive ventricular septal defect with pulmonary stenosis of sufficient severity to impose a resistance to flow greater than that of the systemic peripheral vascular resistance.

The nonrestrictive ventricular septal defect ensures that the pressure in the two ventricles is identical throughout the cardiac cycle under all conditions and that their pressure is the same as that in the aorta throughout the ejection phase. The pulmonary stenosis reduces the pressure and flow in the pulmonary artery and is responsible for a bidirectional or right to left shunt between the ventricles.

Overriding of the aorta is quite variable in degree anatomically and of little importance hemodynamically. Right ventricular hypertrophy is a nonspecific reaction to stress.

Fallot's tetralogy is defined as pulmonary stenosis with a bidirectional or reversed shunt through a nonrestrictive ventricular septal defect.

The term *Fallot's tetralogy* is a misnomer. A more desirable eponymous title would be *Fallot's anomaly*.

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The electrocardiogram in the presence of myocardial infarction and intraventricular block of the left bundle-branch block type†

A clinical pathologic study

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The electrocardiographic identification of myocardial infarction in the presence of left bundle branch block has been reported to be difficult[1, 18] or impossible.[11] Yet this electrocardiographic diagnosis is of importance inasmuch as left bundle branch block is often a complication of myocardial infarction; it was present in 20 (7.7 per cent) of 375 cases of acute occlusion of the coronary artery reviewed by Master and associates.[14] The investigation reported herein was undertaken to provide additional data on the nature and significance of findings encountered when complexes of the left bundle branch block type had been recorded in patients proved to have myocardial infarction at the time of necropsy.

Review of selected literature

Sodeman and associates[17] in 1944 stated: When the septum is extensively damaged the electrical forces produced by its activation are reduced or abolished and the initial negativity of the right ventricular cavity is transmitted to the left and consequently to those regions on the left side of the body that are initially positive in left branch block when the septal muscle is healthy. When this happens Q deflections occur in leads from the left side of the precordium. They may be expected in Lead I also. Several cases have been reported to support this theory.

A Q wave in the leads facing the left ventricle could be caused by normal left to right activation of the ventricular septum if the block causing the prolonged QRS complex were very low in the septum or were in the free wall of the left ventricle.[11] At times it is difficult to distinguish left bundle branch block due to block in the septum from so-called peri-infarction block. Grant and Dodge have

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proposed criteria for making this distinction

An unusual electrocardiographic position of the heart may be attended by Q waves in Lead I and aVL and in leads over the left ventricle. Sodeman and associates[3] noted that a Q wave in Lead I could result if the free wall of the right ventricle faced the right arm. This often occurs in the vertically placed heart in the dog.[13] Lapin and Sprague[5] in 1948 reported on a patient with left bundle branch block who had Q waves in Leads I and aVL and in leads from the left precordium on inspiration only.

Chapman and Pearce in 1957 described several cases of anteroseptal infarction in the presence of left bundle branch block with a rsR' configuration in Lead V₆. They thought that the downward deflection should be called a delayed Q wave delayed by the time necessary for passage of the wave of activation through the septum before it reaches the infarcted area. In some cases the downward deflection did not reach the base line resulting in an R wave with an early deep notch.

Myers and associates believed that Q waves may be present over the right ventricle in the presence of left bundle branch block but without infarction because the right to left activation of the septum may produce a greater negative force over the right ventricle than the positive force produced by the free wall of the right ventricle. They concluded: Thus in cases of left bundle branch block the presence or absence of septal infarction cannot be determined from the contour of the QRS complex in right ventricular lead.

Cabrera and Friedland in 1953 suggested that a notch with a duration of 0.05 sec or more observed in the terminal portion of QRS in the precordial leads that show a morphology rS or Qs (usually V_3 and V_4) is a sign of interoseptal infarction in the presence of complete left bundle branch block.

A Q wave in Lead ... 10 of 28 cases of left ... 1 without clinical ... reported by Dressler ... they stated ... Q wave in Lead ...

block was uncomplicated. They concluded that Q waves or W shaped QRS complexes (or Q wave equivalents) in Lead II are suggestive of posterior infarction in the presence of left bundle branch block.

Kennamer and Prinzmetal[7] in 1956 concluded: In patients with bundle branch block the development of myocardial infarcts involving large amounts of subepicardial muscle may be manifest by a decrease in the magnitude of the R wave in precordial leads overlying the left ventricle or aVF.

Wilson and associates[14] referring to infarction in the presence of left bundle branch block stated: Displacement of the RS-T segment and changes in the T wave may occur if the area of the QRS complex is small. When the area of the QRS complex is large the alterations in the T complex due to infarction are likely to be obscured by those produced by the conduction defect. Experimental infarcts in dogs in the presence of left bundle branch block have resulted in elevation of the S-T segment over the site of the infarct as shown by Kennamer and Prinzmetal.[7]

Definition of terms

Left bundle branch block as an electrocardiographic diagnosis is used in this paper. It does not indicate the site of the disturbance in conduction or the cause. Cases were included in this study if they met all of the following criteria: (1) QRS complex of 0.12 second or greater; (2) sinus origin of the QRS complex; (3) P-R interval of 0.12 second or greater; (4) no S wave in Lead I; (5) broad R wave in left precordial leads or in Lead aVL if the left precordial leads were transitional in form; (6) intrinsicoid deflection starting 0.08 second or longer after the beginning of the QRS complex in leads over the left ventricle; and (7) QS or rS wave forms in Lead V_1 with normal intrinsicoid deflection. The disturbance in conduction in some of the cases may not have been in the septum but peripherally in the left ventricle.

Infarcts were called large when they involved in one continuous area more than one ... of the circumference of the left ventricle ... two of the five slices excluding the ... slice. Infarcts of the ventricular ... were called large if the ...

infarct was transeptal and if more than one half of the septum was involved in two of the five slices excluding the apical slice. Transmural and transeptal infarcts not extensive enough to be called large were called small. Infarcts which occurred 6 weeks or less before the death of the patient were called recent.

Material and method

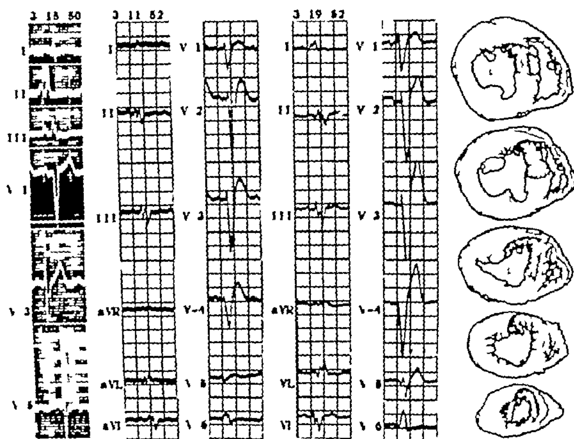
Cases in which necropsy was performed at the Mayo Clinic between January 1947 and April 1959 and in which all of the following characteristics prevailed were selected for this study: (1) a confluent myocardial infarct, either recent or healed, as revealed on examination; (2) availability of electrocardiograms including a minimum of the three standard leads and three precordial leads taken at a time when the infarct was present as judged retrospectively by pathologic examination correlated with clinical findings, and (3) presence of left bundle branch block when the infarct was present as judged by pathologic examination and clinical history. Thirty-nine cases met these criteria. In all cases the heart weighed more than would be expected for the height, body weight and sex of the patient; the mean increase was 100 per cent.

The methods of study and description of the heart in this laboratory have been reported by Edwards.[8] The following were examined to determine the position, extent and age of the infarct: (1) the preserved heart in all but one case, (2) photographs taken at the time of necropsy, and (3) histologic sections taken from the site of the infarct and from all other quadrants of the left ventricle, including the septum. The ages of the recent infarcts were estimated on a histologic basis according to the criteria of Mallory and associates[9] and

*Table I Incidence of certain electrocardiographic changes according to location and size of infarct**

Infarct		Incidence of indicated electrocardiographic change				
Location	S	Q wave in Lead I	Q wave Lead [illegible]	Q wave Q-wave equivalent in Lead [illegible]	R wave Lead [illegible] smaller than Leads [illegible]	Late notch S wave in Leads [illegible]
Anteroseptal	Large	8/13	9 12	9 1	10 13	9/12
	Small	0/10	3/8	0/8	2 10	8
Lateral	Large	1/3	1 3	1 3	0/3	0 3
	Small	0	1 1	0 1	1 2	0 1
Posterior	Large	1/2	1/2	1/2	0 2	1/2
	Small	0/6	0/	9 5	0 6	0 5
Posteroseptal	Large	0 1	0/1	1 1	0 1	0/1
	Small	0 3	1/	0 2	0/3	0 2
Circumferential subendocardial	Large	0 1	0/1	0 1	0 1	1 1
Anterior subendocardial	Large	0/1	0 1	0/1	0/1	0/1
Total number of infarcts		10 4	16/36	1 /36	13 4	11/36
Total number of cases		8/39	14/33	) 33	13/39	1 /33

*[illegible] infarcts [illegible] are represented [illegible]. [illegible] each are expressed [illegible] the number of infarcts [illegible] with [illegible] electrocardiographic change to the number of infarcts [illegible] that change. For example [illegible] 13 [illegible] first column signifies that Q wave was present [illegible] 13 instances in which [illegible] recorded and [illegible] large [illegible] septal infarct was present.



F I Ih t e t (4 ld m died on M h 4 1952 H had experienced severe thoracic pain and l g septal M h 8 195 The heart weight 710 grams expected weight 265 grams V t (I) Lead I V 3 V March 19 1952 th small or absent R wave over the central precordium be f R in Lead V after left bundle branch block and septal infarction

this estimate was correlated with the clinical history in determining the probable date of the infarction. All clinical records were reviewed.

Augmented unipolar limb leads and Leads V V and V were not available for one patient with a large recent anteroseptal infarct and for 5 patients with small infarcts.

Results

Table I summarizes the data obtained in this study. Significant facets of these data are here reviewed.

A Q wave was present in Lead I in 8 of the 39 cases. A large anteroseptal infarct was present in each of these same 8 cases, being recent in 3 (Fig. 1) and old in 5. In addition to a large old anteroseptal infarct, a large recent lateral infarct was present in 1 case (for electrocardiograms in this case see Fig. 8, Case 30 in Reference 4) and a large recent posterior infarct was present in another case (Fig. 2). The septal portion of the infarct was large in 5 cases and small in 3. This evidence indicates that when a patient with myocardial infarction has left bundle branch block associated with a Q wave in Lead I, the infarct will be confined to the interoseptal region or have an anteroseptal component.

How consistently does anteroseptal infarction result in the production of a Q deflection in Lead I when left bundle branch block also is present? In this series, 3 of 6 recent and 5 of 7 old large anteroseptal infarcts were associated with such a deflection. However, of the 24 patients having either a large or a small anteroseptal infarct, only 8 showed a Q wave in Lead I and in all of these 8 patients the infarct was large.

A Q wave was present in Lead aV$_L$ in 14 of the 33 cases in which this lead was recorded A large infarct was present in 9 cases and a small one in the other 5 In 12 of the 14 cases the infarct was antero septal in position Nine of the anteroseptal infarcts were old and 3 were recent In addition to a large anteroseptal infarct a large lateral infarct was present in one case and a large posterior infarct in another case In the 2 cases in which there was a Q wave in Lead aV$_L$ but no anteroseptal infarct the infarct was small and lateral in position in one case and small and posteroseptal in position in the other

This evidence indicates that when a patient with myocardial infarction has left bundle branch block and a Q wave in Lead aV$_L$ almost certainly the infarct involves the anteroseptal or lateral wall of the left ventricle there was only one exception to this generalization in 14 cases

How consistently does anteroseptal or lateral wall infarction result in the production of a Q deflection in Lead aV$_L$ when left bundle branch block is also present? Twelve of 21 instances of anteroseptal infarction and 2 of 4 instances of lateral wall infarction were associated with such a deflection whereas in only 2 of 11 instances in which posterior posteroseptal or circumferential subendocardial infarction was present did a Q wave appear in Lead aV

A Q wave was present in Lead V in 5 of the 33 cases available for study A large anteroseptal infarct was present in each of the 5 cases it was recent in 2 and old in 3 In 1 case a large recent posterior infarct was present in addition to a large old anteroseptal infarct A Q wave was also present in Lead V in all 5 cases whereas in none of the 5 was a Q wave present in Lead V

This evidence indicates that when a patient with myocardial infarction and left bundle branch block has a Q deflection in Lead V the infarct will be confined to the anteroseptal region or have a large anteroseptal component

How consistently is anteroseptal infarction associated with a Q deflection in Lead V when left bundle branch block is present? In this series 5 of 12 patients with large anteroseptal infarction h ch a deflection However of the 21 patients who had either a small or a large anteroseptal infarction and in whom Lead V was recorded only 5 had a Q wave in this lead

An rsR wave form in Lead V$_6$ was present in 2 of the 33 cases available for study a large old anteroseptal infarct with a large septal component was present in both cases and a large recent lateral

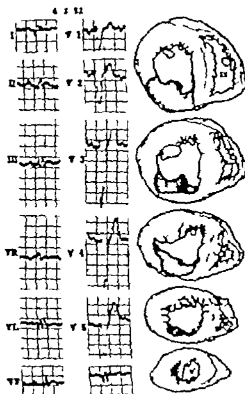


Fig 2 The patient 66- ear-old man died on J ne 1952 He as admitted to the hospital on the day of death because of ankle edema which had been p esent for 1 day and orthopnea present for 3 weeks Necropsy disclosed an old large anteroseptal p cal infarct nd recent large transmural posterior infa ct about 2 day old as judged by histolog examination There as small subendoca dial posterior infarct 4 to 6 eeks old The heart eight as 610 grams expected weight 345 grams Note Q deflection in Leads I V and V The R in Leads V and V is ery small nd lat notching and slurring of the S wav in Lead V are evident Recent posterior infarction may be the cause of the elev ted S-T segment in Leads III and V (Cross sectional diagrams of the heart on he right hand side of the figure are show sected from bov Key to diagrams in this and subsequent figures diagonal shad ng = acute infarction pling = old infarction)

F The pa 6 ea -old ma d d Sep 9 19 8 H had an o d mall terior infarct od old mall be d rdi l p terior u A lar t mural lateral infarct had occurred on Sept 2 19 The h art 46 gram exce ed 50 gram The electrocardiogram of Feb 11 19 8 reveal evide posterior arct f recen more well R es of low oltage in Lead V throu h Lead V p bly related he ld terio farct W h the devel pment of lateral farct and the onset of left bundle br ch block h S-T segment depressed in Lead I and in lead er the left precordium The broad Q wa Lead II III and aV n Sept 19 8 ma be a result of th old anterior and posterior infarcts p the p ere compr en of the recent lateral farction.

infarct was present in addition to the anteroseptal infarct in one of the 2 cases. An early downward notching of the upstroke of the R wave in Lead V_6 in the absence of a Q wave in this lead was present in 2 of the 33 cases available for study; a large anteroseptal infarct with a large septal component was present in both cases and in addition a large recent posteroseptal infarct was present in one of the 2 cases. Thus, the 5 of 12 cases of large anteroseptal infarction in which there was a Q wave in Lead V_6 becomes 9 of 12 cases when instances of Q waves and Q wave equivalents are combined. Furthermore, none of 20 patients without transeptal infarcts had a Q wave or Q wave equivalent in Lead V_6.

The R wave was lower in Lead V_3 or Lead V or both than in Lead V_1 or Lead V or both in 13 of the 39 cases. An anteroseptal infarct was present in 12 of the 13 cases; it was recent in 5 cases and old in 7 and it was large in 10 of the 12 cases. In the thirteenth case a small old lateral infarct and a very small recent anterior apical subendocardial infarct were present.

This evidence suggests that when a patient with myocardial infarction and left bundle branch block has an R wave lower in Lead V_3 or Lead V or both than in Lead V or Lead V or both, the infarct almost certainly is anteroseptal in distribution. Furthermore, this finding appeared in 12 of 24 cases in which there was anteroseptal infarction but in only

1 of 15 instances in which infarcts of other distributions were present

A notch or slur with a duration of 0.05 second or more in the terminal portion of the QRS complex in precordial leads that showed an rS or QS form (usually Lead V_3 or Lead V) was present in 12 of the 33 cases available for study An anteroseptal infarct was present in all 12 cases it was recent in 3 cases and old in 9 cases and was large in 10 of the 12 cases A large posterior infarct was present in addition to a large anteroseptal infarct in 1 case and the infarct was circumferential in another of the 12 cases

A Q wave was present in both Lead II and Lead III in 3 of the 39 cases A small posteroseptal infarct was present in one of these cases a large *lateral* posterior infarct combined with small anterior and posterior infarcts in another (Fig 3) and a small posterior infarct in the third

Electrocardiograms which showed left bundle branch block both before and after a recent infarction were available in 3 cases In 2 cases (Figs 4 and 5) the height of the QRS complex was markedly decreased There was little change in the height of the QRS complex in any of the twelve leads in the third case in which

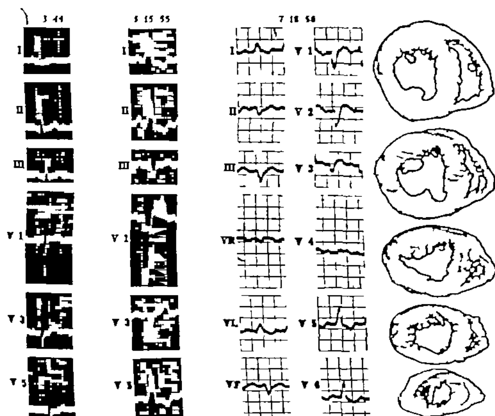


Fig 4 The patient an 88- ear-old man died on July 18 19 8 H had undergone laparotomy on July 7 H had experienced pulmonary edema and chest pa on J ly 18 Left bundle branch block had been present on March 1 1958 A large recen transmural anteroseptal infarct bout 10 day old as judged by hi tologic appearance was found t necrop The heart weight was 5 0 grams expected w ght 294 gram There w marked decrease in the height of the QRS complexes on July 18 1958 as compared with March 15 1955 Note lack of R wav deflection in leads from the right precordium on Jul 18 together with a Q wav in Lead V There is small Q in Lead V on July 18 but none in Leads I or V The nearly isoelectric upright T in Leads I nd V *after* the infarction in marked contrast to the segmental depres ion and T wav inversion in these same leads recorded on March 15 1955 before occurrence of the infarction However this change could be secondary to diminished RS in these lead rather than to an ischemic effect

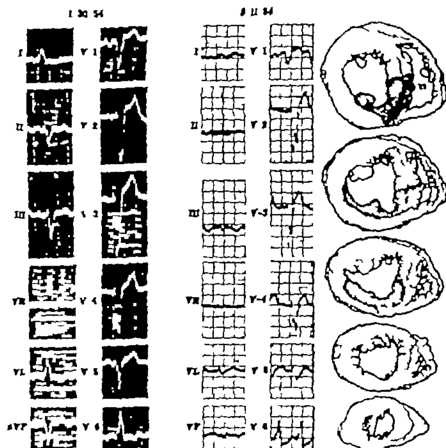


Fig 5 The patient a 59 year-old woman died on Aug 11 1954 Angina pectoris had been present since April 19 and heart failure since January 1954 Necropsy disclosed an old large anteroseptal transmural infarct Left bundle branch block was present before occurrence of a small transmural posteroseptal basal infarction on Aug 10 1954 The heart weight was 650 grams expected weight 306 grams Note marked decrease in the height of the QRS complexes especially in the standard and unipolar limb leads on Aug 11 1954 The Q wave in Lead aVL and Q wave equivalents in Lead V_4 on both January 30 and August 11 and the Q equivalent in Lead I on August 11 are probably related to the extensive septal infarct Note late notch in Lead V on August 11

there was a small transmural posterior infarct

Electrocardiograms taken before a recent infarction but also before the development of left bundle branch block were available in 10 of the 39 cases There was marked reduction in the height of the QRS complexes in Leads V_5 and V_6 in 1 case after a large anteroseptal infarction There was little or no change in the height of the QRS complexes in the other 9 cases even though the infarcts in 4 of the 9 were large and anteroseptal in position

S-T segment changes related to a recent anterior infarction were found in 4 cases However the S-T segment was elevated 1 mm or more in Lead I in only 1 of the 39 cases A small old posterior infarct and a large recent anteroseptal infarct were present in this case (Fig 6) This was also the only case in which the S T segment in Lead V was elevated

S T segment changes believed to be related to recent posterior infarction were found in 3 cases tracings from 2 of which are reproduced in Figs 2 and 3

Comment

The results reported provide a basis for localization of a myocardial scar or infarct in a patient who has such a lesion Because cases of left bundle branch block without

myocardial infarction were excluded from the study, the diagnostic specificity of a certain electrocardiographic finding for infarction or scarring cannot be derived directly from our data. However, strong inferential evidence of infarction would appear to be afforded by certain of these data. The consistent appearance of certain electrocardiographic changes in the presence of a large infarct of uniform location and the absence of these electrocardiographic changes when only a small infarct of similar location or a large infarct of different location was present indicate, we believe, diagnostic reliability of the electrocardiographic finding. Instances of this kind were as follows:

1. A Q deflection in Lead I occurred in 8 of the 39 cases. In each of these cases a large transmural anteroseptal infarct was present. A Q wave did not occur in 26 cases (total of 39 minus 13 with large transmural anteroseptal infarcts) in which a large anteroseptal infarction was lacking.

2. A Q deflection or a Q wave *equivalent* was present in Lead V_6 in 9 of 33 cases in

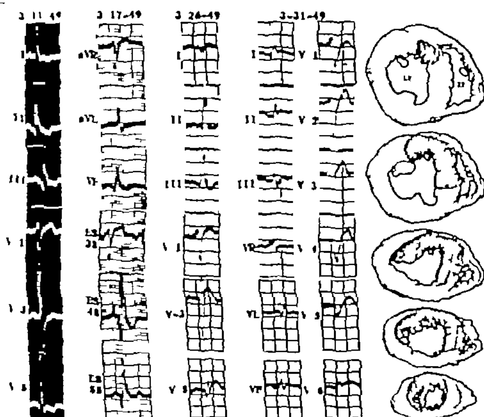


Fig. 6. The patient, a 65-year-old man, died on April 2, 1949. He had had angina pectoris since July, 1948. He became cyanotic on March 22, 1949, while undergoing abdominal operation. Necropsy revealed an old small transmural posterior infarct and a recent large transmural anteroseptal infarct about 10 days old as judged by histologic appearance. The heart weight was 740 grams (expected weight, 415 grams). In the electrocardiograms of *March 11 and March 17* note the Q waves in Leads II, III, and aVF and in esophageal leads with prolonged QRS in these leads, indicating posterior infarction with postinfarction block. On *March 24, 1949, after anteroseptal* infarction, there is no R wave in Leads I and V_1, and the QRS complex is prolonged in these leads, probably indicating anterior postinfarction block. On March 31, 1949, the QRS interval has again increased and a major change has occurred in the mean QRS in the frontal plane. A Q wave is no longer present in Leads III and VF but is present in Lead I, aVL, and V_6. Note the almost absent R wave in Lead V_1 and the late notch and slurring in Lead V_1 on March 31, 1949, and the suggestion of elevation of the S-T segments in Leads I and V_6, the T wave being upright.

which this lead was recorded. In each of these 9 cases a large transmural anteroseptal infarct was present. Such deflections did not occur in 21 cases (total of 33 minus 12 with *large transmural anteroseptal infarcts*) in which a large anteroseptal infarct was lacking.

Of somewhat lesser reliability are the instances in which a certain electrocardiographic finding occurred predominantly in the presence of a large infarct of uniform location but occurred also in instances in which a small, similarly located infarct was present. Into this category would fall instances of the following types:

1. An R wave in Lead V_3 or Lead V_4 or both lower than an R in Lead V_1 or Lead V_2 or both occurred in 13 of 39 cases. A large anteroseptal transmural infarct was present in 10 of these 13 cases, a *small anteroseptal infarct in 2 additional* cases, and a small old lateral infarct accompanied by a very small recent apical subendocardial infarct in the other case.

2. A notch or slur with a duration of 0.05 second or more in the terminal portion of the QRS complex in precordial leads that showed an rS or QS form was present in 12 of 33 cases available for study. In all of these 12 cases an anteroseptal infarct was present; in 9 the infarct was large and transmural, in 2 it was small, and in 1 it was large but subendocardial.

3. A Q wave was present in both Lead II and Lead III in 3 of 39 cases. A large lateral posterior infarct was present in one of these cases, a small *posteroseptal infarct* in one case, and a small posterior infarct in the third.

Of least reliability are those instances in which a given deflection occurred usually in association with a large infarct of uniform location but not infrequently in association with small infarcts of the same location and occasionally in association with infarcts of entirely different location. Into this category would fall instances in which there was a *Q* deflection in Lead aV_L. This deflection occurred in 14 of 33 cases, in 9 of which there were large transmural anteroseptal infarcts, in 3, small anteroseptal infarcts, in 1, a small lateral *infarct*, and in 1, a small *posteroseptal* infarct.

Summary of data for all three of the categories just reviewed discloses that 24 of the 39 cases included in this study presented one or more of the electrocardiographic findings held to afford evidence of greater or lesser *reliability of myocardial* infarction. Of the 18 cases in which infarcts were large, 15 presented one or more of these electrocardiographic findings, whereas 9 of 21 cases in which infarcts were small so qualified.

Summary

On the basis of a study of the pathologic, electrocardiographic, and clinical data in 39 cases in which there was a confluent myocardial infarct in the presence of left bundle branch block, the following observations are made:

1. Substantial evidence of transmural anteroseptal myocardial infarction in the *presence of left bundle branch block would* appear to be afforded (a) by a Q deflection in Lead I or (b) by a Q deflection or Q wave equivalent in Precordial Lead V_6.

2. Supportive evidence of anteroseptal myocardial infarction in the presence of left bundle branch block would appear to be afforded (a) by an R wave in Lead V_3 or Lead V_4 or both that is lower in amplitude than an R wave in Lead V_1 or Lead V_2 or both or (b) by a notch or slur with a duration of 0.05 second or more in the terminal portion of the QRS complex in precordial leads that shows an rS or QS form.

3. Supportive evidence of infarction involving *the posterior wall of the left ven*tricle in the presence of left bundle branch block would appear to be afforded by a Q deflection in Standard Leads II and III.

4. Equivocal evidence of anteroseptal infarction in the presence of left bundle branch block would appear to be afforded by a Q deflection in Lead aV_L.

5. In two of three instances in which electrocardiograms showing left bundle branch block were recorded both before and after myocardial *infarction*, the height of the R waves in the standard leads decreased markedly.

6. Changes in S-T segments and T waves of a degree to be considered suggestive of myocardial infarction occurred in a minority of cases in which myocardial infarcts were recent.

7 The weight of every heart was more than the weight expected for the height body weight and sex of the patient The mean increase in the weight of the heart over the expected weight was 100 per cent

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High frequency components in the electrocardiograms of normal subjects and of patients with coronary heart disease

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A wide band recorder with an expanded time scale for recording the electrocardiogram reveals high frequency components in the QRS that do not appear in the conventional electrocardiogram. The greater incidence of such high frequency components in patients with coronary heart disease when compared with a group of normal subjects used as controls was first reported in 1953[1] and subsequently confirmed.[2,3]

High frequency components in the QRS recorded with adequate instrumentation consist of small fast notches, slurs, and segments of high velocity. These phenomena, which are 1 to 7 milliseconds in duration, have been quantified by means of both high pass and low pass electronic filters.[4] It is the purpose of this paper to report on the number of high frequency notches and slurs in the electrocardiograms of 104 patients with clinical evidence of coronary heart disease as compared with the incidence of these high frequency components in 100 normal subjects who served as controls.

Materials and methods

One hundred four subjects with clinical evidence of coronary heart disease were studied. Eighty eight had well documented histories of myocardial infarction and typical electrocardiographic changes. The other 16 had the clinical symptoms of angina pectoris on exertion with normal electrocardiograms when at rest but definitely positive postexercise electrocardiograms. None of the patients had evidence of congenital, rheumatic, or syphilitic heart disease. The ages ranged from 43 to 75 years with a mean of 56 years. There were 92 male and 12 female subjects. All of these were fully ambulatory. Approximately one half of the group were normotensive and none was severely hypertensive since we intentionally excluded the latter from this study. Sixty four had normal heart size by x ray examination whereas 40 showed slight to moderate enlargement. Twenty six patients were receiving digitalis. The electrical axis in the frontal plane ranged from +80 to −60 degrees. Subjects with bundle branch block were excluded from this study.

The control group consisted of 100 individuals who were free from cardiovascular disease as determined by past history, present signs or symptoms. There were 95 male and 5 female subjects. The age range was 40 to 65 years with a mean of 52 years.

With the technical assistance of Harry L. Flem.
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Electromedical Laboratory, The Moore School of Electrical Engineering, University of Pennsylvania [illegible]

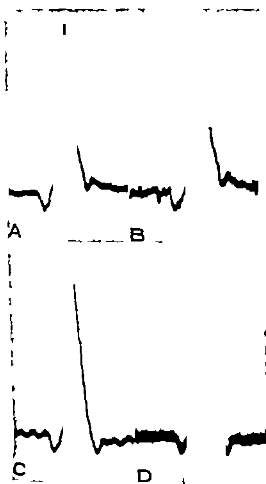


FIG 1 *A* Original signal Lead II *B* The original signal plus muscle tremor induced by tensing the right forearm *C* The original signal plus 60-cycle interference seen in the base line *D* The original signal plus 120-cycle interference seen in the base line. In these records there is no significant notching or slurring of the R wave despite base-line noise

The heart size was normal by x-ray examination and the conventional electrocardiogram was negative The electrical axis in the frontal plane ranged from +90 to −10 degrees All members of this group are designated as normal in the tables of this paper and Appendix II

Twelve scalar leads from the standard electrode positions were made with a wide band recorder having a frequency response flat to 1 000 cycles per second and down 6 decibels at 5 000 cycles per second as previously described This is in sharp contrast to most direct writing electrocardiographs now in use which are relatively unresponsive at 100 cycles per second The amplification was regulated so that the QRS deflection traversed about 75 per cent of the cathode ray screen Thus all the leads were made as large as possible The relative size of any lead was determined by the height of its accompanying millivolt standardization signal

An expanded time scale was obtained by using a paper speed of 350 mm per second which is 14 times the speed of the conventional electrocardiogram Records were made with Kodak Linagraph Paper No 697 which is 5 inches wide This was microfilmed and projected on a screen at

*See Appendix II [illegible] frequency response [illegible]

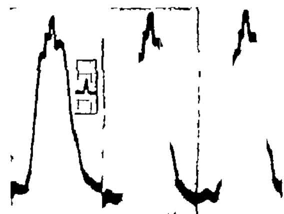


FIG 2 Illustrates three marked notches near the peak of the P wave There is also slight slurring at the peak and on the down stroke of the R wave Three successive complexes are shown to demonstrate the repetitive nature of the high frequency components The small complex was made with a direct writer



FIG 3 Illustrates two notches in the Q waves, seven notches and or slurs in the R waves The complexes are shown to demonstrate the repetitive nature of the high frequency [illegible] small complex [illegible] made with [illegible] d[illegible]

Table I. High frequency components in limb leads

Number of components	Lead I				Lead II				Lead III				aVR				aVL				aVF				Largest limb lead	
	N		A		N		A		N		A		N		A		N		A		N		A		N	A
	S	L	S	L	S	L	S	L	S	L	S	L	S	L	S	L	S	L	S	L	S	L	S	L		
0	30	32	8	20	8	47	6	7	14	10	5	2	18	48	9	23	19	14	3	6	6	21	3	3	68	24
1	16	13	3	13	1	22	6	13	12	5	3	6	6	12	11	11	13	5	7	8	5	20	7	5	21	18
2	3	2	4	15	6	12	9	23	22	3	16	11	2	6	5	11	20	3	16	11	11	16	19	8	10	19
	1		3	8	3	2	10	10	15	3	53	11	1		7	5	7		5	7	5	7	13	10	1	21
4			8	5			3	4	6		6	4	1		1	2	1		5	3			5	3		
							1	3	2		6	3				1			1	3			1	1		4
6								1											1				2			

N, Normal; A, Abnormal; S, Small Lead; L, Large Lead.

Table II. High frequency components in precordial leads

Number of components	[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]	
	N	A	N	A	N	A	N	A	N	A	N	A
0	41	4	51	19	5	21	0	34	81	33	83	35
1	30	17	23	19	29	19	13	15	8	19	4	27
2	16	2	20	37	11	23	14	16	4	19	3	21
3	8	27	6	15	8	23	1	11		16		9
4	2	5		6		7		8		6		6
	1	3		2		3		6		1		
6				1		1		3				

N, Normal; A, Abnormal.

close range by means of a wide angle lens so that the record for final viewing was 15 inches tall, or three times the size of the original photograph. This technique greatly facilitated reading, because it eliminated the need for rolling and unrolling yards of unwieldy paper, and because it enlarged the original record. The time scale of the record when this optical system was used was very close to 1 millimeter per millisecond.

In the rapidly moving portion of the QRS there are notches and slurs that are

*For those interested in [illegible] 35 mm. trans-parent [illegible] recommended in place of the [illegible] paper used by us. [illegible] can be used to [illegible] the record to any desired size. [illegible] in recording [illegible] of 200 to 300 mm. per second [illegible] will be used to preserve [illegible] wave.

Table III. Combined total of high frequency components in V, V and largest limb lead

Number of patient	Number of abnormal subjects	Number of normal subjects
0	11	66
1	8	16
2	10	11
3	10	5
4	13	
5	8	
6	11	
7	4	
8	8	
9	5	
10	1	
11	3	
12	1	

equaled or even exceeded by the width of the base line Therefore it is necessary to take precautions that a true heart signal is present rather than an artifact due to noise To identify true cardiac potential one can make use of their repetitive characteristic in successive QRS complexes Only notches or slurs which are clearly repetitive in several successive cycles are read as true cardiac potentials On the other hand artifacts usually due to muscle tremor occur at random and the notching in each successive QRS complex is in a different form and place With experience there is no problem in distinguishing between artifacts and true cardiac potentials of high frequency However if marked muscle tremor is present due to dyspnea shivering anxiety thyrotoxicosis neurologic disease or senility the record usually becomes unreadable for high frequency components because they are masked by the noise This is true for both direct visual inspection of the time voltage records and for spectral analysis [4]

Fig 1,A shows Lead II of a healthy 20 year-old woman without signs or symptoms of heart disease There are no significant high frequency components present in the QRS Fig 1,B shows the same lead as Fig 1,A plus self induced muscle tremor C and D of Fig 1 show the same lead as A plus increased base line noise due to 60-cycle and 120-cycle interference respectively introduced from an oscillator Artifacts of this amplitude in the base line produce no significant high frequency alteration in the R wave If the base line shows noise in excess of that shown in B to D of Fig 1 the tracing is usually considered to be unreadable for high frequency components unless they are distinctly larger than the noise and of course clearly repetitive

Results

Table I shows the number of notches and slurs in each of the limb leads for the normal and abnormal groups The number of subjects for each lead totals less than 104 for the abnormal group and less than 100 for the normal group This is because there was sufficient muscle tremor in a few leads to render them unreadable for high frequency components and in a few instances a simple failure in photographic technique caused the lead to be indistinct In either case such a lead was omitted from Table I

In the limb leads there is a distinction made between the three larger leads and the three smaller leads because notching is more common in smaller limb leads in both normal and abnormal subjects as has been reported previously Among the limb leads the lead of largest amplitude which has an axis collinear with the direction of the maximal frontal plane QRS vector gave the best discrimination between the normal and the abnormal individuals since only one normal subject had three slurs in this lead whereas 32 abnormal subjects had three or more notches and or slurs Table II shows the number of notches and or slurs in the precordial leads Of the precordial leads V_4 and V gave the best discrimination in that no normal individual had three or



Fig 4 The upper QRS complexes are normal They V and V taken 2 years before infarction The lower QRS complexes are V and V from the same individual 3 months after well-documented episode of myocardial infarction The appearance of high frequency components including very fast deflections in the lower QRS complexes is self-ev

more notches or slurs whereas among the abnormal subjects there were 23 who had three or more such high frequency components in V_1 and 17 who had them in V_4 (see Fig 2) Leads V V_4 and V_4 offered some discrimination when the number of notches considered to be abnormal was raised to four per lead (Fig 3) The number of high frequency notches and/or slurs per subject were counted for the combined total in Leads V_1 V_4 and the largest limb lead (see Table III) In the normal group no individual had a combined total of five or more high frequency components in these three leads In the abnormal group 41 had a combined total of five or more notches and/or slurs in these three leads with a maximum of twelve and a mean of seven In the 16 subjects with angina pectoris and normal resting conventional electrocardiograms 7 had three notches in either the largest limb lead V_1 or V_4 Each of the same 7 subjects had a combined total of five or more notches and/or slurs in these three critical leads

Development of high frequency notches or slurs may appear as a serial change occurring during myocardial infarction as illustrated in Fig 4 High frequency serial changes have occurred in all of the 5 patients in whom we had an opportunity to obtain a wide band expanded record before and after infarction

Discussion

On the basis of our results it seems reasonable to establish as the upper limit of normal two distinct high frequency notches and/or slurs per lead for Leads V_1 V_4 and the limb lead of greatest amplitude The normal limit for the combined total of high frequency components in these three leads is four per subject There is a high probability that a subject who has more than two high frequency components in one of these leads and more than four for all three leads and who falls in the age groups studied has coronary heart disease The mathematical derivation of these probabilities is given in Appendix II

The occurrence of serial change in the high frequency electrocardiogram deserves serious consideration because it appeared to be due to coronary heart disease in the 5 cases observed by us It is very possible that rheumatic myocarditis and other myocardial diseases which result in fibrotic changes can also produce both high frequency components and serial changes but we have not studied these diseases

Judging from our subjects with angina pectoris it is probable that for pre employment life insurance or other types of examinations where symptoms may be denied about 40 per cent of the subjects with early coronary disease and negative conventional electrocardiograms will show high frequency change when the method described in this paper is used Therefore this could serve as a diagnostic adjunct in detecting the probability of coronary heart disease The normal group reported upon in this paper with the addition of subjects each year will serve in time to determine whether this method is of value for prognosis in people without known signs or symptoms of coronary heart disease

Our figures do not relate to the gravity of prognosis or ultimate mortality but to the probability that disease is or is not present Even with 104 patients we have had insufficient time and inadequate exposure to establish a valid ratio of mortality However certain statements do seem justified The increase in incidence of high frequency notching of the electrocardiogram in coronary disease seems more than can be explained by coincidence or chance fluctuation and therefore requires another explanation In the absence of pathologic evidence of our own we must draw on that of others in analogous situations Durrer and associates[7] used a wide band recorder and an expanded time scale and studied experimental myocardial infarction with intramural and epicardial electrodes They found abundant notching in the electrocardiogram They stated that the excitation wave was desynchronized and fragmented and that notching was due to dissimilar rates of conduction of the excitatory process Burch Horan Ziskind and Cronvich have shown that there are changes in the vectorcardiogram not readily apparent in the conventional electrocardiogram in subjects with myocardial infarction They found these changes due to smaller less solid lesions Zoll Wessler and Blumgart[8] have reported that in

angina pectoris patchy necrosis or fibrosis is a common lesion We believe that comparable myocardial defects are most probably responsible for the abnormal number of high frequency notches and slurs in the electrocardiograms of subjects with coronary heart disease

Summary

Through the use of electronic and photographic equipment capable of recording a wide band of frequencies from 0.01 to 5000 cycles per second it has been shown that subjects with clinical evidence of coronary heart disease have a much greater incidence of high frequency notching and slurring in the electrocardiogram recorded with this high fidelity equipment than do apparently normal subjects The diagnostic possibilities of this method are discussed

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Appendix I

David B Geselowitz Ph D

This paper deals with the occurrence of notches of between 1 and 7 milliseconds duration in the electrocardiogram of human beings Such notches will not be observed in tracings recorded on most conventional electrocardiographs unless they are very large in amplitude a d en in this case they will be grossly attenuated and distorted In order to determine the frequency requirements of a system including an amplifier and recorder which will satisfactorily pass notches of short duration the following analysis was undertaken

A simple low pass filter is a network consisting of a single resistor and capacitor as shown in Fig 5 This network has frequency response

$$\frac{1}{1} = \frac{1}{\sqrt{1 + (2\pi fRC)^2}} = \frac{1}{\sqrt{1 + 3(f/\ )^2}}$$

which falls to a value of one half at the 6 decibel frequenc f where

$$f = \frac{0.275}{RC}$$

and fall off at a rate of 6 decibels per oct e for frequencies mu h greater than f

As a represent ti notch consider a tria gular pulse of u t amplitude and duration T as show in Fig 6 This pulse i described m thematically as

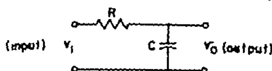


Fig 5 Simple low pa filter t (R) and a capacitor (C)

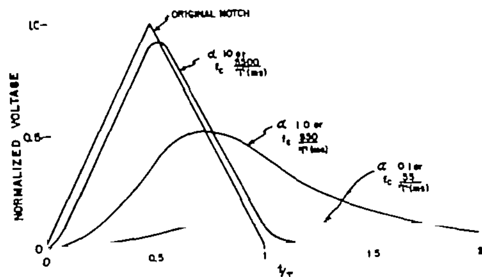


Fig. 6 Response of low pass filter with different 6 decibel cutoff frequencies f_c measured in cycles per second to triangular notch of duration T. Duration T and time t are measured in milliseconds.

$$V = \begin{cases} 2\frac{t}{T} & \text{for } \frac{T}{2} > t > 0 \\ 2-2\frac{t}{T} & \text{for } T > t > \frac{T}{2} \\ 0 & \text{for } t > T \text{ or } t < 0 \end{cases}$$

The change in this pulse after it passes through the filter can be calculated on the basis of techniques of transient circuit analysis. The resulting output V_0 is found to be

$$V_0 = \begin{cases} 2\frac{t}{T} - \frac{2}{\alpha}(1 - e^{-\alpha t/T}) & \text{for } \frac{T}{2} > t > 0 \\ 2 - 2\frac{t}{T} + \frac{2}{\alpha}\left[1 + (1 - 2e^{\alpha/2})e^{-\alpha t/T}\right] & \text{for } T > t > \frac{T}{2} \\ \frac{2}{\alpha}(1 - 2e^{\alpha/2} + e^{\alpha})e^{-\alpha t/T} & \text{for } t > T \end{cases}$$

where

$$\alpha = \frac{T}{RC} = \frac{f_c T}{0.275}$$

The result clearly depends on the parameter α which in turn is related to f_c. Plots of V_0 for $\alpha = 0.1$, 1 and 10 are shown in Fig. 6. For a fixed pulse duration output falls as the width of the band … decreased.

This effect is even more dramatic if … notch is superimposed on the ascending … descending portions of the R wave. Fi… illustrates this point. Here a notch of 2 milliseconds duration is shown superimposed on an R wave which falls from … peak value to 0 linearly in 30 milliseconds. The notch is taken to have an amplitude of 10 per cent of that of the R wave. In part a the original signal is shown. The notch itself is shown at the base line. It is interesting to observe that the notch when superimposed on the R wave undergoes an apparent reduction in amplitude. This effect is enhanced as the pulse duration increases and affords an explanation for the results described in connection

with Fig 1 *B* in the text where moderate tremor in the base line was not apparent in the QRS

The results of parts *b* and *c* are taken from data in Fig 6 For f = 1 100 c p s the notch is reproduced quite well (*b*) whereas for f = 110 c p s it is reduced more or less to a slur (*c*) For f = 11 c p s there would be no discernible effect of the notch on the R wave as a matter of fact the R wave itself would be distorted

Whereas most systems have frequency responses which fall off more rapidly than 6 decibels per octave the present results are representative of those that would be obtained in general for a low pass filter As a rule of thumb then we conclude that to pass a notch without appreciable distortion a low pass filter must have a 6-decibel frequency f measured in cycles per second of

$$f > \frac{2.5}{T} = \frac{2\,500}{T\,(ms)}$$

while for

$$f < \frac{0.1}{T} = \frac{100}{T(ms)}$$

the notch may be missed entirely For intermediate values the pulse will be attenuated and distorted accordingly

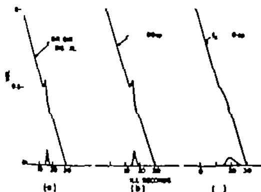


Fig 7 Response of low pass filter to triangular notch of duration 2 5 milliseconds superimposed on descending R wave for various values of filter cut off frequency f_c (*a*) Original signal or f infinite (*b*) f = 1 100 c p s (*c*) f = 110 c p s Small pulse on base line represents the notch itself

Appendix II Statistical analysis of significance of high frequency notching

J Alan Lauer A S A

Leads V_4 V and the largest limb lead were studied in greater detail because it appeared that the differences in the data for the normal and abnormal groups were greatest for these leads Simple mathematical curves were fitted to the data for these leads reported in Tables I II and III These curves serve to smooth out the random fluctuations in the reported data and also provide a means to extrapolate the data for normal subjects in order to estimate the probabilities of normal people having a high number of notches Two characteristics of the data created some difficulty in fitting these curves These were the small number of groups for the normal subjects (a maximum of 4 groups because only 0 1 2 or 3 notches were observed on any one of these leads) and the tendency to show about the same number of people with 1 notch as with 2

Exponential curves of the type Y = AB were fitted to the distributions for the normal subjects of notches on each of the three leads and also to the distribution for the normal subjects of the sum of the notches on the three leads Third degree curves ($Y = ax^3 + bx^2 + cx + d$) were fitted to the distributions for the abnormal subjects of notches on Lead V_4 and the largest limb lead and second degree curves ($Y = ax^2 + bx + c$) were fitted to the distributions for the abnormal subjects of notches on Lead V and the sum of the notches on the three leads The curves in all cases were fitted by the method of moments

The chi square (χ^2) test was applied to these fitted curves in order to test

From the A ... D ... Pr ... d ... M ... al ...
... C ... f Medical ... Ph ... 1

Table IV. Probability of having a given number of notches on Lead V, Lead V, or the largest limb lead

Number of notches	Lead V		Lead V		Largest limb lead	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
0	8454	3561	9048	3628	6944	2503
1	130	2061	0861	2636	2122	2220
2	0702	1904	0082	1 99	0648	2019
3	0031	1839	0008	1119	0198	1739
4 or more	0006	0635	0001	0818	0088	1514

Table IVA. Probability of having a given total number of notches on Lead V, Lead V, and the largest limb lead

Number of notches	Normal	Abnormal
0	6 11	1078
1	2353	1101
2	0892	1104
3	0338	1056
4	0128	1047
5	0049	0989
6	0018	0911
or more	0011	2694

Table V. Probability that a person with a given number of notches on Lead V, Lead V, or the largest limb lead falls in the abnormal class*

Number of notches	Lead V	Lead V	Largest limb lead
0	04	04	01
1	15	25	10
2	51	71	26
3	87	94	49
4 or more	93	99	65

*From [illegible] probability [illegible] for the hypothetical [illegible] known except the number of notches on the specified lead or, in the case of Table VA, the sum of [illegible] on the three leads.

reasonableness of the fit. The test indicated an acceptable fit for Lead V of the normal subjects, largest limb lead of the abnormal subjects, and the combination of the three leads for the normal subjects, and an excellent fit in the remainder of the cases except Lead V of the normal group. In this last instance it was not possible to apply the test since there were only three groups (0, 1, or 2 notches) and two of them were very small. However, the fitted curve appears to be a reasonable one for estimating the probability of a normal person having more than 2 notches on this lead.

Probabilities that a member of the normal or abnormal group would show a given number of notches on a given lead or the combination of three leads were determined from the fitted curves. These probabilities are shown in Tables IV and IVA.

In order to determine the probability that a person with a given number of notches does or does not have coronary heart disease, it was necessary to estimate

Table VA. Probability that a person with a given total number of notches on Lead V, Lead V, and the largest limb lead falls in the abnormal class*

Number of notches	Probability
0	0
1	05
	17
3	29
4	49
5	69
6	85
7 or more	96

*From [illegible] the number of notches on the specified lead or, in the case of Table VA, the sum of [illegible] on the three leads.

Table VI Expected distribution of 1 000 people according to the number of notches on each of Lead V₁, Lead V₆ and the largest limb lead

Number of notches	Lead V₁ Normal	Lead V₁ Abnormal	Lead V₆ Normal	Lead V₆ Abnormal	Largest limb lead Normal	Largest limb lead Abnormal
0	760 9	35 6	814 3	36 3	675 0	25 1
1	117 6	20 6	77 5	26 3	191 0	2? 2
2	18 2	19 0	7 4	18 0	58 3	20 2
3	2 8	18 4	7	11 2	17 8	17 4
4 or more	5	6 4	1	8	7 9	15 1
Total	900 0	100 0	900 0	100 0	900 0	100 0

Based [illegible] Tables V and VA

the proportion of the population from which these samples were drawn which would fall in the abnormal class. A study of the health records of the employees in the Home Office of the Provident Mutual Life Insurance Company indicates that 10 per cent would be a reasonable estimate of this proportion. On the basis of this proportion and the probabilities in Tables IV and IVA, the probabilities in Tables V and VA were calculated. These tables support the conclusion in the paper that any member of the population represented by this study who shows more than 2 distinct high frequency notches and or slurs on any one of the three leads in question or a total of more than 4 such high frequency components on these three leads is very likely to have coronary heart disease.

Tables VI and VIA were derived as a byproduct of Tables V and VA and are shown here as a matter of possible interest. They show for a random sample of 1 000 people the expected number of people in the normal and abnormal classes with a given number of notches based on the same assumptions as Tables V and VA.

Table VIA Expected distribution of 1 000 people according to total number of notches on Lead V₁, Lead V₆ and the largest limb lead

Number of notches	Normal	Abnormal
0	559 0	10 8
1	211 8	11 0
2	80 3	11 0
3	30 4	10 9
4	11 5	10 5
5	4 4	9 9
6	1 6	9 1
7 or more	1 0	26 8
Total	900 0	100 0

Based [illegible] Tables V and VA

Morphology of the human atrioventricular node, with remarks pertinent to its electrophysiology

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The electrophysiology of the atrioventricular node and bundle of His has been the subject of numerous recent interesting investigations[1,2] As a result of these studies two unsettled questions have emerged (1) whether there is a system of dual transmission in this region and (2) the nature of the slight delay in conduction observed in or near the A V (atrioventricular) node Morphologic research in this field has not kept pace with the elegant physiologic studies This is a report of morphologic observations on the A V node and its environs in which particular attention was focused on those details which could contribute to a better understanding of its electrophysiology

Material and Method

Eighty-one hearts from human subjects were studied Three of the 81 were from infants whereas the remainder were from adults who were between 18 and 82 years of age Both normal and abnormal hearts were included One or more electrocardiograms had been recorded in 76 of the subjects shortly before death

For examination of the A V node a bloc of tissue which extended from the noncoronary sinus of the aorta to the epicardium of the crux of the heart was removed this bloc included at least 2 cm of the interatrial and the interventricular septa From this bloc of tissue slices 2 mm thick were cut perpendicular to the atrioventricular valve rings which is also perpendicular to the junction of the interatrial and interventricular septa From the aortic end of the bloc the first 6 to 10 slices usually included the undivided A V bundle and the A V node Both of these structures may sometimes be seen with the naked eye since they are located beneath the right atrial endocardium just posterior to the membranous portion of the interventricular septum[33,34]

As with the sinus node which was also studied in each case[35] a variety of stains was employed but the most useful proved to be the Goldner modification of the Masson trichrome[36] Photomicrographs were obtained with a Zeiss photomicroscope

Results

For a representative concept of its shape the A V node of the human being may be thought of as a flattened oblong structure concave on one side and convex on the other somewhat like a tiny spleen (Figs 1 and 2) The concave surface lies directly

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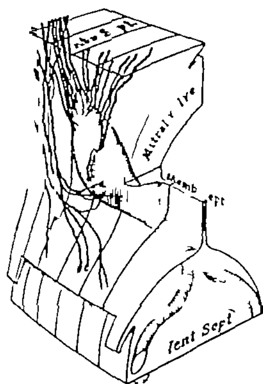


Fig. 1. A schematic drawing of the human A-V node illustrating its relationship to the two atrioventricular valves and the interatrial and interventricular (including its membranous portion) septa. The A-V bundle divides into a single right bundle branch and multiple left bundle branches as usual. Fibers from the central interatrial septal tracts and from the Eustachian ridge enter the posterior superior margin of the node and also form bypass tracts as described in the text. Note that some of the bypass tract fibers re-enter the inferior margin of the node and that some terminate at the base of the tricuspid valve; rarely some penetrate directly into the crest of the interventricular septum.

on the right atrial side of the central fibrous body, which is the anchor of the mitral annulus. The average dimensions of the A-V node in an adult human being are approximately 1 by 3 by 6 mm, but there is considerable variation in its size.

The posterior and superior margins of the node receive fibers from adjacent atrial myocardium. From the anterior and inferior margins of the node a bundle of parallel fibers (the bundle of His) come together and veer into the middle of the central fibrous body, at the same time descending toward the interventricular septum. In the central fibrous body the bundle of His measures about 1 mm on cross section. When the bundle of His reaches the crest of the interventricular septum it becomes roughly triangular in cross section. It continues anteriorly to divide into the right and left bundle branches. The precise course of these branches has been well defined in several animals (notably the cow and sheep) but is more difficult to trace in man.

Within the center of the A-V node there is usually a major artery, but this is less constant in either its presence or its central location than is the sinus node artery.[3] The substance of the node is almost entirely a profusely ramifying and interlacing group of striated fibers which are shorter and broader than sinus node fibers (Fig. 3). There is little collagen matrix in the A-V node, in contrast to the heavy concentration of collagen in the normal sinus node. At the anterior inferior end of the node the interlacing fibers become oriented parallel to each other to form the A-V bundle.

Two groups of fibers from the interatrial septum enter the A-V node from above and behind. The first group courses down the center of the interatrial septum and divides into two tracts just above the node. The larger tract passes directly into the node; the smaller tract deviates toward the right atrial endocardium. The second group of fibers comes primarily from the Eustachian ridge and also divides into two small tracts: one tract continues down the right atrial endocardium, bypassing the A-V node, whereas the other tract turns centrally to join the central septal fibers entering the posterior superior portion of the node. There is a decussation of tracts as the fibers from the Eustachian ridge turn centrally to cross those from the septum which turn toward the right atrial endocardium (Fig. 4). The septal tracts which turn to the right atrial endocardium join with the tracts from the Eustachian ridge which bypass the A-V node (Figs. 5 to 11).

There are numerous Purkinje fibers (Fig. 12) in all these tracts but also ordinary appearing myocardial fibers which do not possess these characteristics. In the tracts descending from the Eustachian ridge down the right atrial endocardium around the A-V node there are numerous Purkinje fibers. These bypass tracts divide as they descend to the base of the tricuspid valve, which is virtually always

Fig. Three views of the A V node and its environs from the heart of a 18 year old boy. In A the central fibrous body, which is the anchor of the mitral valve (MV), lies between the interatrial septum (IAS) and interventricular septum (IVS). Opposite the mitral valve in the right atrial endocardium along the left margin of the photograph. Just beneath the right atrial endocardium lying directly on the central fibrous body is the A V node. Tracts from the interatrial septum can be seen entering the node at the upper arrow, which is the bypass tract may be seen joining the inferior margin of the node at the lower arrow. The bypass tract lies between the node and the right atrial endocardium and fibers from them may be seen continuing to the bottom of the photomicrograph en route to the base of the tricuspid valve, which is out of the range of the photograph. B is a view of the upper portion of the node shown in A. Tract from the left atrium ... fibers occupy the upper left portion of the photomicrograph, descending along the right atrial endocardium to bypass the A V node as indicated by the arrow. Tract from the interatrial septum occupy the upper right portion of the photomicrograph and descend into the A V node. Between the two tracts there is a lacy net of interlacing fibers (see text for discussion). In this and all subsequent photomicrographs, AVN indicates A V node. C is a view of the lower portion of the ... The bypass tract between the A V node and the endocardium of the right atrium are shown re entering the inferior margin of the node which occupies most of the central portion of this photomicrograph from top to bottom. (All stained with Goldner trichrome stain. A ×4, B ×10, and C ×25.)





Fig 3 Fou ws demon tin he en ral architecture of the normal hum A V node A F om a 60 yr -old man B From 56- ea ld man C nd D F om 57 yea -old man Not the interconn ctions arborizations (All tained th C kloer tri hrome A ×64 B ×100 C ×64 nd D ×100 [all])



Fig 4 A view of the region between the lower interatrial septum and upper A V node from the heart of a 49 year-old man Decussation of the interatrial septal tracts which turn toward the endocardium and of the tract from the Eustachian ridge which turn toward the upper margin of the A V node are well shown The bypass tracts (*BPT* here and in subsequent photomicrographs) pass vertically down the left margin of the photomicrograph between the A V node and right atrial endocardium

below the level of the A V node and considerably below the attachment of the mitral valve (on the opposite side of the central fibrous body) The two major divisions of the bypass tracts are into one group which re-enters the inferior margin of the A V node and a second group which terminates often in a whorl at the base of the tricuspid valve Rarely a few fibers from the bypass tracts penetrate directly into the crest of the interventricular septum these were present in one heart from an adult and one heart from an infant in this study (Fig 13) The only other direct communication of atrial with ventricular fibers not passing through the A V node was encountered posterior to the A V node in the hearts of two adults these passed from central interatrial septal tracts directly through to the crest of the interventricular septum

The posterior margin of the A V node is never far from the opening of the coronary sinus and sometimes directly abuts it The anterior margin of the A V node is almost inseparable from the A V bundle the most convenient distinguishing feature being the point at which the fibers cease interlacing and become parallel a point at which the structure also veers centrally into the central fibrous body The bundle continues for about 10 mm in its descent to the crest of the interventricular septum before it begins dividing This descent of the A V bundle occurs along the posterior inferior margin of the membranous interventricular septum (Fig 1)

Discussion

The microscopic anatomy of the normal human A V node may help explain certain aspects of the electrophysiology of A V conduction Two pertinent anatomic features are the bypass tracts in the right atrial endocardium and the profuse arborization of the fibers composing the node itself This latter feature is well known

In Kistin's[11] study of the morphology of the A V node he noted the region here referred to as bypass tracts but stated that this was ordinary atrial myocardium In at least half of the present cases however this region was predominantly composed of well-defined Purkinje fibers Since sections were made only at 2 mm intervals the possibility that *all of the hearts* contain *Purkinje fibers in these bypass tracts* cannot be excluded

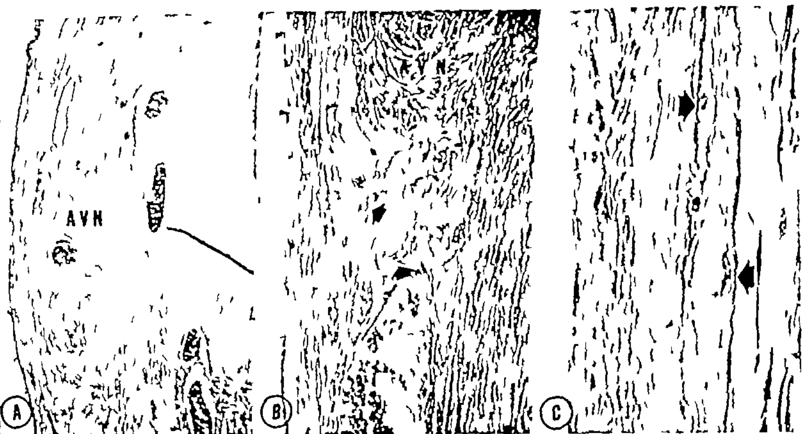
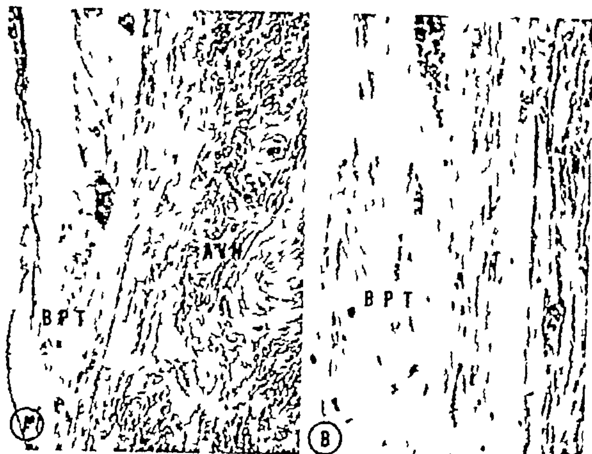


Fig. 3. Three views of the AV node and its bypass tract from the heart of a 38 year old man. A is an orienting view showing the AV node between the central fibrous body and the right atrial endocardium. B is a view of the lower portion of the same node with arrows indicating the connections between the node and the bypass tract, which can be clearly seen passing along the right atrial endocardium. C shows some of the fibers from the bypass tract illustrating their Purkinje-like characteristics of coarse myofibrils and clear perinuclear zone (*arrows*). (All stained with Goldner trichrome. A ×10, B × 3 and C ×160.)



Fr 6 In iew of the A V node and b pa tracts from the heart of 64 ear-old ma Orientatie n 4 imilar t that in Fig 5 A this ph otomicrograph of the pper portion of the node I B the comparati e izes f the lar P rkinje fibers in the b pa tract nd the mall fiber in the A V node re well b (Both are tained with Goldner trichrome A × 25 B × 64)

It is widely accepted that rapid conduction occurs in Purkinje fibers whether rapid conduction may also occur in fibers not possessing this morphology is uncertain Thus the absence of Purkinje fibers in the right atrial endocardial bypass tracts of some human hearts prevents one from assuming that all these tracts conduct rapidly but it does not exclude the possibility

If the bypass tracts do conduct rapidly as the presence of Purkinje fibers suggests they are an obvious route by which an impulse may circumvent the A V node Such an impulse could re-enter the inferior margin of the node and bypass directly to the A V bundle If there is dual conduction in the bundle such a premature arrival of a bypassing impulse might produce premature excitation of one of the bundle branches especially the right However with current techniques no morphologic characteristic has been found that suggests dual conduction in the A V bundle which instead appears to be a uniform sheath of similar fibers Its morphology does not exclude such a physiologic possibility

A large number of the hearts in this study were from patients in whom extensive electrocardiographic studies had been made including electrocardiograms twice daily for as long as 2 weeks In none of these patients were there any electrocardiographic changes that suggested the Wolff Parkinson White phenomenon although anatomically most of them had bypass tracts which contained Purkinje fibers It is obvious that the presence of such tracts does not mean that they regularly carry an impulse around the A V node to excite the A V bundle prematurely Therefore it must be assumed that their function of rapid conduction and bypass of the A V

node if it exists is intermittent This is not incompatible with current electrophysiologic observations

In their study of the physiology of AV conduction Moe and co workers postulated a dual AV conduction system the tracts of which communicated with each other They proposed that impulse cancellation could occur through these communications rendering one of the pathways inoperative This is entirely consonant with the morphology described here such cancellation conceivably occurs at several points The first of these is at the posterior margin of the node where tracts from the interatrial septum and from the Eustachian ridge meet or decussate The second is at the junction of the bypass tracts with the inferior margin of the node However to presume cancellation at the latter point it would be necessary for the impulses passing through the node and through the bypass tract to travel at approximately the same speed Otherwise more rapid conduction in the bypass tract would produce excitation of the AV bundle before the impulse through the AV node could arrive there in such a case simultaneous

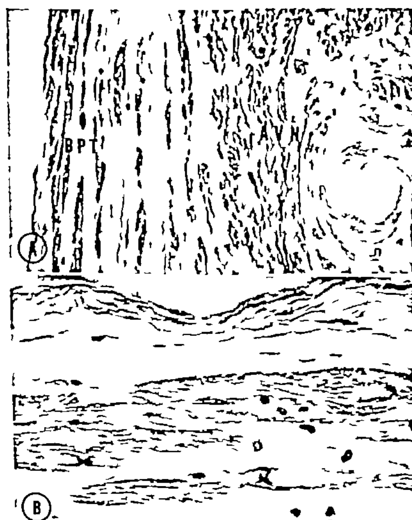


Fig 7 Three views of the AV node and bypass tracts from the heart of 7 year-old man Orientation in 1 similar that in Fig 5 4 I B the Purkinje characteristic of fibers the bypass tract are shown I C (on p 764) the bypass tract (BPT) are shown te minating t the base of the tricuspid al (TI) (All tained th Goldner trichrome 1 ×25 P ×160 and C ×10)



[illegible]

spread of the impulse both down the A-V bundle and back up the A-V node might cause retrograde cancellation in the latter. Finally, in some A-V nodes there is an outer layer of relatively straight nonanastomosing fibers; an impulse traveling in them might reach the inferior margin of the node at the same time that an impulse via the bypass tracts did, which would produce cancellation.

Although numerous observers have documented a delay in A-V conduction which occurs in the region of the A-V node, there is some debate whether this occurs in the node or at the atrionodal junction. Morphologically there is nothing about the tracts in the interatrial septum or Eustachian ridge near the A-V node which would suggest decelerated conduction. The structure of the node, however, suggests a mechanism of delay there. If one can presume that impulse cancellation may occur when two juxtanodal tracts meet, the same type of cancellation may occur within the node.

With the exception of a few relatively straight fibers in the outer layer of the node, all the other fibers are short and ramify to anastomose with each other profusely. An impulse entering such a labyrinth of pathways must be divided and rerouted many times, even if conducted without interruption. If a divided impulse follows fibers which later rejoin, cancellation may occur. This circuitous pathway of an impulse wandering within the node is supported by the observations of Pruitt and Essex, who noted a broad "hump" in electrograms recorded from the node in contrast to a sharp biphasic spike in those from the A-V bundle. Similar wide



[illegible]



Fig. 8. Two views of the A-V node and bypass tracts from the heart of 53-year-old man. Orientation is similar to that in Fig. 1. A Purkinje fiber from the bypass tract is shown in B. (Both stained with Goldner trichrome. A ×25 and B ×160.)

Fig. 9. Views of the A-V node and bypass tracts from two different hearts. A is from the heart of a 29-year-old woman and B is from the heart of a 44-year-old woman. The relationships of the bypass tracts and the A-V node are well shown in A. In B some of the bypass tract fibers are cut transversely and others obliquely or longitudinally; this variation in course is not unusual. Also in B a few of the fibers in the middle of the node seem to be descending directly instead of arborizing (frequently); this is unusual. (Both stained with Goldner trichrome. A ×10 and B ×25.)

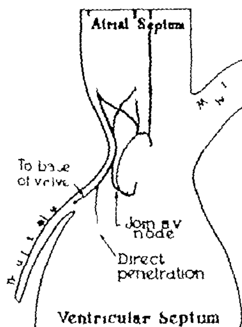


Fig. 13. A d[illegible]ng f[illegible]m [illegible] represent[illegible] sections of normal human A-V node with its relationship [illegible] the bypass tracts. Orient[illegible] the same [illegible] Figs. 1, 2 and 11.

complexes have been recorded from the A-V node by Scher and his colleagues.

Such a slowing of the normal impulse when it arrives in the A-V node, with the possibility of a rapid bypass tract parallel to the node, is the reverse of the suggested dual system of Moe and his colleagues. In their proposal it was the normal pathway which conducted rapidly, whereas the conduction in the bypass tract was delayed. Because of a postulated delay in the bypass tract, they were unable to employ their hypothesis to explain the Wolff-Parkinson-White syndrome, although they could explain reciprocal rhythm and paroxysmal supraventricular tachycardia. By means of their same reasoning, the present findings on the morphology of the node and its environs can be used to explain all three of these electrocardiographic phenomena, since the present findings suggest that conduction would usually be more rapid in the bypass tract than in the A-V node.

Additionally, if conduction delay does occur within the node because of multiple cancellation, it is possible to explain both accelerated and delayed A-V conduction through an injured A-V node. If the injury is focal, normal cancellation or deviation of the impulse in the interconnecting fibers may be prevented, and conduction may occur in a straighter, more direct route. This is illustrated by the finding of both shortened and prolonged A-V conduction in acute posterior myocardial infarction. The supply of blood to the crux of the heart, which is compromised in true posterior infarctions, is also the supply of blood to the human A-V node.

In the same manner, focal lesions within the node can establish a dual conduction system, even without consideration of the bypass tracts. It has been postulated above that the normal delay in A-V conduction occurs within the A-V node and is caused by a multiple cancellation effect. If focal disease within the node involves predominantly one half, the other half would still be subject to the normal amount of this interference in conduction, whereas the diseased half may have a sufficient number of interconnections removed to permit a more direct conduction of an impulse (Fig. 14). From this postulated basic division of conduction within the labyrinthine internal structure of the pathologic node, one may construct explanations for reciprocal rhythm and the Wolff-Parkinson-White phenomenon in the same manner as with the dual conduction system hypothesis of Moe and others. It is not so strange that an impulse in the normal A-V

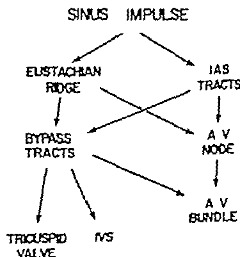


Fig. 14. Schem[illegible] ch[illegible]rt [illegible]ting the path[illegible] [illegible]hich an impulse ma[illegible] f[illegible]ll[illegible] from th[illegible] sin[illegible] n[illegible]de to the A-V bundl[illegible] and [illegible] th[illegible] all main [illegible] [illegible] bypa[illegible] the A-V [illegible]e. Th[illegible] ch[illegible]rt suppl[illegible]ment the data presented [illegible] Fig. [illegible] and 11.



Fig 17 A group of Purkinje fibers from the beodocardium of the Eu t chian ridge depicting the cla r character tics f these fibers Compare to the Purkinje fibers how from the bypas tract in the preceding figures (Goldner trichrome stain ×160)

node sometimes becomes delayed or ac celerated but that it is normally tran mitted with such regularity and consis tency

Although the present findings do not exclude the possibility of other mecha nisms of production of the Wolff Parkinson White syndrome [43] for example conduction through a bundle of Kent [44 45] they make it unnecessary to employ such an explana tion It is significant that Purkinje fibers have not been described n instances in which a Kent bundle was identified the bundle has always consisted of ord nary myocardium [43 4] Even though fibers which have the appearance of ordinary myo cardium may be capable of rapid conduc tion (as in the human A V bundle) that possibility has never been proved in man E idence from electrocardiographic and vectorial studies is at the very best quite indirect It would lend support to the bundle-of Kent theory f someone would demonstrate Purkinje fibers in a bundle of Kent since there is good evidence that Purkinje fibers conduct at a apid rate

If electrophysiologic studies confirm that the bypass tracts described here actually do operate as an alternate A V conduction system then add tional co siderations will be necessary in regard to the exact function of the A V node The suggestion has al ready been made that it may only be an alternate pacemaker which otherwise has no function The suggestion has also been made that it is an electronic oscillator which feeds impulses into the A V bundle at the same rate as does a neighboring dominant oscillator the sinus node These and similar theories will require more care ful examination

Certain phylogenet considerations lend credibilit to the sign ficance and function of these human bypass tract In the Hunterian Lecture of 1942 Davies[43] pre sented his result of a study of the conduct ng system of ertebrate and an hearts Both Davies[4] and Sir Arthu Keith[44] had long been nterested in the conduction system of birds because of certain func tional requirements due to their rapid heart rate the a erage heart rate of a canary is 1 000 beats per m nute The tri cuspid valve which is a del cate fibrous structure in mammals is a strong muscular ring in birds Because of the rapid entric ular rate in the bird t is necessary for the tricuspid valve to close actively by muscu lar contraction rather than passively as in the mammal in order to prevent retro grade regurgitation of ventricular blood For this to happen there must be a more rapid conduction of the sinus impulse o the muscular tricuspid ring than t



Fig. 13. Photomicrograph of the lower A-V node and upper interventricular septum from the heart of an infant. Some of the bypass tract fibers continue directly into the septum (*arrow*). Although only a few hearts from infants were studied, this finding does not seem to be uncommon in these hearts, suggesting that fibrous demarcation between atria and ventricles is more distinct in the adult heart. (Goldner trichrome stain. ×25.)

ventricular myocardium and it was the pathway of this impulse which Davies defined. Although there are some differences between the disposition of this bypass tract in birds and that in man (as there are also differences in the topography of the A-V node), there are also basic similarities. In particular, the termination of some of the bypass tract fibers at the base of the tricuspid valve in man are suggestively similar. What the function of these fibers near the tricuspid valve is in man can only be conjectured at the present time. If they carry impulses at all, one must even consider whether they carry impulses to or away from the tricuspid ring.

In addition to Davies' observations in birds, de Carvalho and de Almeida[4] have described a somewhat similar structure in the rabbit, which they designate the *sinoatrial ring bundle*. They believe that this structure can undertake pacemaker functions and emphasize its regular termination over the atrial border of the atrionodal junction. Speculating that this ring was a remnant of the embryonic A-V ring, they suggest that it may contribute certain delaying properties to A-V conduction. Whether this reasoning may be applied to A-V nodal electrophysiology in man remains to be determined. The frequency of the Wolff-Parkinson-White phenomenon in Ebstein's anomaly[1] suggests that this may be a human analogy.



Fig. 14A. (For parts B, C, and D, see opposite page.)

In the dog a large mass of fibers is present between the AV node and the right atrial endocardium (Fig 15) Whether these function as a bypass tract is unknown Most electrographic studies in this region of canine hearts have employed either plunge electrodes inserted into the AV node or surface electrodes sutured directly to the right atrial endocardium Both of these methods may injure the bypass tracts of the dog if they exist Studies employing nontraumatic electrodes are needed to record electrograms from the endocardium over the AV node which can be compared with simultaneous records obtained from within the node (perhaps by means of a plunge electrode placed from the left atrial side) These should help elucidate the problem of whether impulses travel in a bypass tract and what the relation of such conduction is to electrical activity in the AV node

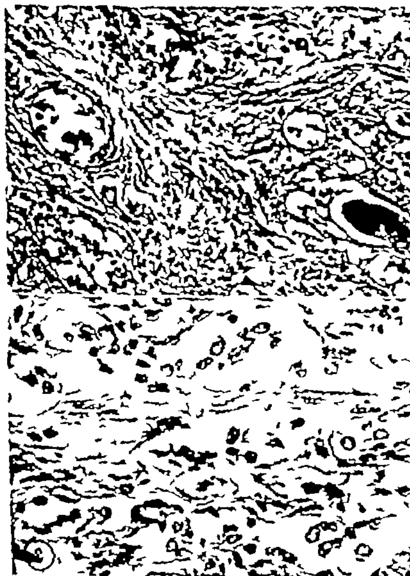


Fig 14 Photomicrographs of the pathologic A V nodes from two patients with (A) hemochromatosis and (B and C) hypernephroma metastatic to the AV node The disruption of normal interconnection of fibers is apparent (A Iron reaction counterstained with safranin ×205 B PAS ×64 C Goldner trichrome ×160)



Fig. 13. Photomicrograph of the lower AV node and upper interventricular septum from the heart of an infant. Some of the bypass tract fibers continue directly into the septum (arrow). Although only a few hearts from infants were studied, this finding does not seem to be uncommon in these hearts, suggesting that fibrous demarcation between atria and ventricles is more distinct in the adult heart. (Goldner trichrome stain, × [illegible].)

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In addition to Davies' observations in birds, de Carvalho and de Almeida[4] have described a somewhat similar structure in the rabbit, which they designate the *atrioventricular ring bundle.* They believe that this structure can undertake pacemaker function, and emphasize its regular termination over the atrial border of the atrionodal junction. Speculating that this ring was a remnant of the embryonic AV canal, they suggest that it may contribute certain delaying properties to AV conduction. Whether this reasoning may be applied to AV nodal electrophysiology in man remains to be determined. The frequency of the Wolff-Parkinson-White phenomenon in Ebstein's anomaly[?] suggests that this may be a human analogy.



Fig. 14A. (For parts B and C [illegible])

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Electrocardiographic alterations after neurosurgical procedures

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The influence of the central nervous system on the function of other systems has been the subject of extensive investigation. In this respect the cardiovascular system has received considerable attention at both the experimental and the clinical levels. In particular, electrocardiographic changes have been reported in a variety of abnormal cerebral states, especially after cerebrovascular accidents. Electrocardiographic changes have been observed in the course of experimental stimulation of various cortical and subcortical areas of the brain and in the course of experimental trauma and cerebral compression.

Reports have appeared concerning the electrocardiographic changes during various operative and diagnostic neurosurgical procedures.[18] The changes recorded in these clinical studies relate mainly to changes in blood pressure and disturbances in cardiac rhythm.

During the last 2 years we have been impressed with the frequent and striking electrocardiographic changes which occur after diagnostic, operative, and combined neurosurgical procedures. In contrast with previously reported observations, our findings consisted mainly of prolongation of Q-T and alterations in the T and U waves. Arrhythmias were not a common finding in this study. We report these observations in the hope that they may help elucidate the complex regulatory mechanism of the central nervous system on the function of the cardiovascular system.

Material and methods

A total of 3 consecutive patients were studied during the period from November 1958 to May 1960. The procedures performed on these patients are listed in Table II.

Each patient had a complete 12 lead electrocardiogram preoperatively on the day preceding the neurosurgical procedure. Postoperative tracings were taken on an average of 2 to 4 hours after completion of the procedure and in most instances for several days subsequently. In a few subjects stabilization of the electrocardiogram or return to the preoperative state did not occur for several weeks. These patients were followed up by the taking of frequent tracings. A notation was made concerning the state of nutrition of each patient prior to hospitalization, occurrence of vomiting, presence or history of cardiovascular disease, and administration of drugs known to alter the electrocardiogram. Serum sodium and potassium were determined by the flame photometric method. Serum chloride was determined by the

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titration method.[14] Calcium was determined by the Clark-Collip method and phosphorus by the Fiske-Subbarrow method.[1,2] The range of normal for this laboratory is as follows: chloride 94 to 108 mEq. per liter; sodium 134 to 144 mEq. per liter; potassium 3.5 to 5.3 mEq. per liter; calcium 9 to 11.5 mg. per cent and phosphorus 2.5 to 4.5 mg. per cent.

The ventriculograms and pneumoencephalograms were obtained by the replacement method employing local anesthesia for the ventriculograms and general anesthesia for the pneumoencephalograms.

We studied each electrocardiogram separately. The degree of prolongation of Q-T was determined for the preoperative and for each of the postoperative tracings. This was accomplished by comparing the actual Q-T interval with the predicted Q-T interval as determined by the formula of Bazett.[16] The Q-T interval was obtained from the precordial leads since Leads V_2, V_3 and V_4 gave the clearest demarcation of the end of the T wave. At times the U wave merged with the terminal limb of the T wave. In these cases no attempt was made to separate the Q-T interval from the Q-U interval. The Q-T interval was considered to be significantly prolonged when its duration exceeded 20 per cent of its predicted value.

Table I summarizes pertinent clinical information concerning each of the subjects. The preoperative clinical cardiac evaluation including determinations of blood pressure, electrocardiogram and chest x-ray film was normal for the entire group except for 3 patients. Patients 17 and 35 had hypertension and cardiac enlargement. Patient 21 had coronary artery disease. These 3 patients had abnormal electrocardiograms.

Results

The ages of our patients ranged from 6 weeks to 68 years with an average of 38.7 years. There were 17 female and 20 male patients.

Table II tabulates the incidence of the electrocardiographic alterations after the various neurosurgical procedures.

The three most prominent and frequent changes consisted of prolongation of the Q-T interval, alterations in the T wave and prominence of the U waves. There were 17 patients who showed Q-T prolongation as determined from the formula of Bazett. The increase ranged from 5.3 to 107 per cent with an average increase for the entire group of 42.6 per cent. Q-T prolongation of a significant degree (20 per cent or more) occurred in 15 patients for an incidence of 41 per cent. Of the various procedures, Q-T prolongation was observed most frequently in those patients who were undergoing a craniotomy with or without ventriculography. Of 12 such patients, significant prolongation was observed in 7 for an incidence of 60 per cent. The measured Q-T interval exceeded the predicted Q-T interval in the preprocedural electrocardiograms by 20 per cent in only 2 patients. These 2 patients showed additional prolongation of a significant degree after the neurosurgical procedure.

The T wave alterations ranged from a significant decrease in amplitude of the T wave to partial inversion. This occurred in 28 patients for an incidence of 76 per cent. The altered T waves were frequently widened which suggested incorporation of the U wave. It is to be noted that 3 patients had abnormalities of the T waves before the procedure. In Patient 35 the T waves were originally inverted and became upright after pneumoventriculography. The inverted T waves in Patient 21 became more deeply inverted after craniotomy. Patient 17 originally showed flattening of the T waves and there was no change after pneumoventriculography. Patient 25 had a normal electrocardiogram and after a craniotomy for metastatic malignancy developed ECG changes compatible with a subendocardial myocardial infarction.

Prominence of the U wave was not present in any of the tracings taken preoperatively and developed in 18 patients after the procedure, an incidence of 48.7 per cent. It was particularly prevalent after pneumoencephalography and craniotomies.

The fourth most frequent finding was a pronounced sinus arrhythmia which occurred in over one third of the patients who underwent ventriculography and pneumoencephalography.

Other alterations in the electrocardiograms were not a prominent finding in our cases and are listed in Table II.

Table 1 Clinical data

Patient number	Procedure	Age (years) sex	Clinical diagnosis	Neurological deficit	Spinal fluid	[illegible]		[illegible]
						[illegible]	[illegible]	
1	Pneumoencephalography	16 M	[illegible]	None	Normal			Normal
2	Pneumoencephalography	9 F	[illegible]	None	Normal			Normal
3	Pneumoencephalography	17 F	Epilepsy	[illegible]	Normal			Normal
4	Ventriculography	19 M	[illegible]	[illegible]	Normal			Normal
5	Ventriculography	6 M	[illegible]	[illegible]	Increased pressure [illegible]	[illegible]	[illegible]	Normal
6	Ventriculography and [illegible]	61 F	Occipital [illegible]	[illegible] right [illegible]	Increased pressure	[illegible]	[illegible]	Normal
7	Ventriculography	40 F	Brain tumor suspect	[illegible] papilledema	Increased pressure	[illegible]	[illegible]	Normal
8	Pneumoencephalography	27 M	Epilepsy	None	Normal			Normal
9	Pneumoencephalography	41 F	[illegible]	[illegible]	Normal			Normal
10	Frontotemporal craniotomy, right	59 M	Chromophobe pituitary adenoma	[illegible]	Not [illegible]	[illegible]	[illegible]	Normal

11	I neu ncephalog ph	13 I	\ ty ction Iru su pect	Stu I	N I		CO 17 \ 130 Cl 97 K 3 9	N nal
1	Suboccipital craniotomy	5 M	Cy tic tmcytom left cerel llur	I palle lemn t \	Incre ed pre sure		CO 2(Cl 95 \ 137 K 4 5	Norm l
13	Front l cr niotom right	56 F	Old urachnoiditis d chrs m	Bli lne optic tr phy	Not studied			\ rmal
14	I neumoencephalogr phy	31 M	Bmm tumor u pect tem l carotid ufficiency	\ mbne enkn of left arm	I rotein 91 mg % pre sure 270 mm			Normal
15	\ triculograph and parietal ectom right	43 M	Bra dise met t he from fu k	I tn B ln k left foot papilledem	Incre sed pre sure	CO 22 Cl 98 Na 130 K 4 6	CO_2 26 Cl 93 Na 131 K 4 6	Norm l
16	\ triculography	64 M	C rebral arteriosclero	H adaches	Normal			Norm l
17	I nc m xentriculography	34 M	H perten encephal path	At su po t e Roml rg	\ rmal			Su pected ly po t t M t test blood pres re 1 0/100 mm Hg
18	I neumoen ph logr phy	49 F	Idiop thic epilepsy	At su po tive Roml rg	\ rmal			Normal
19	I neumoenc ph logruph	15 F	Convul n t t	\ ne	\ rm l	(O_2 4 (I 9) Na 110 K 3 7	CO 3 (I 98 \ 138 K 3 4	Norm l
20	\ triculography	30 F	B t mor u pect	None	Normal			Norm l

Ca I P ere I d l so pre t
CO_2, Cl, Na and K re rec rd d in mEq per liter
tle l ls l id d 776 and 777

Table 1 Clinical data—Cont d

Patient number	Procedure	Age (yr) sex	Final diagnosis	Neurological findings	Spinal fluids	Electrolytes Preop	Electrolytes Postop	Cardiovascular status
21	Frontoparietal craniotomy left	51 M	Frontal lobe glioma left	B bi ki left cent l faci l kne	Increased pressure 400 mm		CO 30 Cl 3 N 141 K 4 6 C 9 I 4 0	I erted I w es
	Ventriculography	54 F	Cerebral atrophy	Bil teral h perrefl	I rot 5 mg			Normal
3	Ventriculography and suboccipital craniotomy	58 M	Met ta is to brain from pulmonary neoplasm	V rtigo poor coordination pos tiv Romberg	Negativ	CO 3 Cl 101 N 135 K 4 0	CO 3 Cl 95 N 135 K 3 5	Normal
4	Ventriculography and temporoparietal craniotomy right	5 M	Parietal glioblastoma multiforme right	P pilledema hemi paresis left	N t tu lied		CO 30 Cl 94 N 135 K 3 9	Normal
	Frontoparietal crani otomy right	50 M	Meta tasis t brain from pulmonary neoplasm	Bell palsy right hemiparesis left	Not tudied		CO_2 0 Cl 95 N 139 K 4 9	After craniotomy les k ped antero-lateral subend card al infarction
26	Pneumoencephalography	19 F	Post traumatic cephalalgia	Neg tiv	Normal		CO 4 Cl 99 N 14 K 4	Normal
	Ventriculography	33 M	Headaches after craniotomy	Severe he dache	I re ure 10 mm	CO_2 3 Cl 103 N 135 K 3 6		N rm l
8	Ventriculography	56 M	Arachnoiditis of posterior fossa	P pilledem scot m t	Increased p ure			N rm l

29	V tric l graphy	65 M	Cortical roph	Motor lo l lat l lesion t t	N l			Normal
30	Pneumoenceph lography	6 F	Idiopathic epilepsy	None	Negat	C 10		Norm l
31	Frontotemporal cranio tom left	55 F	Sphenoid ridge meningioma recurrent	Hemiparesis right	Not t ted			Normal
3	Ventriculog ph	55 M	Cortical atroph	H m pare right d orie tation	Increa d protei 87 mg	CO_2 19 Cl 105 N 135 K 4 1	CO_2 16 Cl 98 N 132 K 3 4	Norm l
33	Pneumoencephalograph	56 M	Temporal lobe t mor left	Hemiparesis right	Normal	CO 4 Cl 101 Na 140 K 4 1	CO 21 Cl 101 Na 136 K 3 9	Normal
34	Frontoparietal craniotomy left	4 F	Frontal lol dermoi l cyst	Negativ	Normal	CO_2 29 Cl 94 Na 135 K 4 4	CO_2 6 Cl 91 Na 137 K 4 2	Norm l
35	Pne mo nc l g ph	42 F	H pertensive cere bros lar disea e	Hem pare is right d orienta	Norm l	CO_2 21 Cl 10 N 143 K 4 0	CO 20 Cl 104 N 139 K 4 1 I 3 4 C 10	Larg heart hyper tension 210/1 0 mm Hg f w e n rsion
36	Pne moencephalogr phy	39 F	Occ pitop rietal arachnoiditis right	H dache con lus st t	Norm l		CO_2 27 Cl 93 N 13 K 4 0 C 10 9 I 3 25	Compla ned of chest pain w th li tion to left arm
37	V triculography and Temporal craniotomy left	56 M	Temporal lobe spong oblastom left	Hem pare right	Not tudied	CO 1 Cl 100 N 139 K 4	CO_2 4 Cl 101 Na 140 K 3 9	N rmal

Table I Clinical data—Cont'd

Patient number	Procedure	Age (yr.) sex	Final diagnosis	Neurological findings	Spinal fluids	Electrolytes Preop.	Electrolytes Postop.	Cardiovascular status
21	Frontoparietal craniotomy, left	53 M	Frontal lobe glioma, left	Babinski, left; central facial, Loeos	Increased pressure 400 mm.		CO_2 30 Cl 97 Na 141 K 3.6 Ca 9.7 P 4.0	Inverted T waves
22	Ventriculograph	54 F	Cerebral atrophy	Bilateral hyperreflexia	Protein 52 mg. %			Normal
23	Ventriculography and suboccipital craniotomy	58 M	Metastases to brain from pulmonary neoplasm	Vertigo, poor coordination, pos. Romberg	Negative	CO_2 23 Cl 103 Na 155 K 4.0	CO 25 Cl 98 Na 135 K 3.5	Normal
24	Ventriculography and temporoparietal craniotomy, right	57 M	Parietal glioblastoma multiforme, right	Papilledema, hemiparesis, left	Not studied		CO 30 Cl 94 Na 135 K 4.8	Normal
2	Frontoparietal craniotomy, right	50 M	Metastases to brain from pulmonary neoplasm	Bell's palsy, right; hemiparesis, left	Not studied		CO 20 Cl 98 Na 129 K 4.9	After craniotomy developed anterolateral subendocardial infarction
26	Pneumoencephalography	18 F	Post-traumatic cephalalgia	Negative	Normal		CO 4 Cl 99 Na 14 K 4.7	Normal
27	Ventriculography	33 M	Headaches after craniotomy	Severe headache	Pressure 210 mm.	CO 3 Cl 103 Na 135 K 3.6		Normal
28	Ventriculography	56 M	Arachnoiditis of posterior fossa	Papilledema, scotoma	Increased pressure			Normal

29	Ver ricul raphy	68 M	C I ar l s	Motor lo I I l orien on I	N			\ 1
30	I neumo ncephalog phy	6 F	Id or thic ep lep s	None	Ne t	Ca 10		Normal
31	Fron o mporal cran ot y left	38 F	Sphcno d ri lge meningioma recurrent	Hemip resis right	Not st 1 1			Normal
3	Ventriculography	35 M	Cortical trophy	Hem pare is right d orient tion	Increa d protei 87 mg	CO_2 19 Cl 105 Na 13 K 4 4	CO 16 Cl 98 \ 13 K 4 4	Normal
33	Pneumoencephalograph	56 M	Temporal lobe tumor left	Hemiparo is right	Normal	CO 24 Cl 101 \ 140 K 4 1	CO 3 Cl 101 \ 136 K 3 9	\ rmal
34	Frontoparietal craniotomy left	47 F	Frontal lobe dermoid cyst	Negati	Norm l	CO_2 29 Cl 94 Na 135 K 4 4	CO_2 26 Cl 94 Na 137 K 4 2	Normal
35	Pneumoventriculograph	42 F	Hypertensive cere brovascular disease	Hemiparcsi right d arthria	Normal	CO_2 1 Cl 102 \ 142 K 4 0	CO_2 20 Cl 104 Na 139 K 4 1 I 3 4 C 10	Large heart hyper ten ion 240/170 mm Hg T av inversion
36	Pneumoencephalography	39 F	Occipitoparietal arachnoiditis right	H adache m ulc stat	Norm l		CO 27 Cl 93 \ 13 K 4 0 C 10) I 3 25	C mpla ned of chest pa n with ad tion t left rm
7	V triculography and temporal craniotomy left	56 M	Temporal lobe spongioblastoma left	Hemipare right	\ t tudied	CO 4 Cl 100 \ 139 K 4 2	CO_2 24 Cl 101 \ 140 K 3 9	\ rm l

Table II. Incidence of ECG alterations after various neurosurgical procedures

	Pre-operative	Pneumoencephalography	Ventriculography	Pneumoventriculography	Ventricular craniotomy	Craniotomy	Total	Per cent
Number of patients	37	13	10		5		37	100.0
Alteration in T wave	3	8	8	2	4	6	8	75.6
Prominent U	0	7		1	4	4	18	48.6
Prolongation of Q-T interval	2	6	4	0	4	3	17	45.9
Sinus arrhythmia	0	5	3	0	1	0	9	24.3
Alterat[illegible] T wave	1	2	1	0	2	1	6	16
Changes QRS electrical axis	0	1		1	1	1	6	16.2
Alteration S-T segment	0	1	1	0	2	2	6	16
Sinus bradycardia	0	2	2	0	1	0	5	13.5
Sinus tachycardia	0	0	1	0	4	0	5	13.5
Extrasystoles	0	3	2	0	0	0		13.5
Large upright T wave	0	1	0	0	1	0	2	5.4
Low QRS voltage	0	0	0	0	1	0		5.4
Coronary sinus rhythm	0	1	0	0	0	0	1	2.7

The duration of the electrocardiographic changes ranged from 2 to 6 days; in a few patients the alterations persisted for a longer period of time.

Examples of the chief electrocardiographic abnormalities are shown in Figs. 1 to 4.

Discussion

In contrast to the previously reported alterations in the electrocardiogram after cerebrovascular accidents and surgical removal of brain tissue,[4-8] the analysis of the changes in patients who underwent our studies provided a less complex and more physiologically intact setting for studying cerebrocardiac relationships.

In considering the possible cause or causes of the electrocardiographic changes observed in our material, several possibilities have to be considered. The electrocardiographic changes observed simulate alterations frequently associated with disturbances of electrolyte balance. Electrolyte disturbances have been implicated by some workers as a possible explanation for the electrocardiographic changes which follow cerebrovascular accidents. Other investigators have presented evidence against this concept.[8] In reviewing our

material we were unable to demonstrate any correlation between the depletion of serum electrolytes and the changes in the electrocardiogram. The possibility, however, that some of the changes in the electrocardiogram are a reflection of alterations in electrolytes at the cellular level cannot be discarded.

Some authors have attributed the electrocardiographic changes which follow cerebrovascular accidents to primary myocardial alterations of ischemic origin involving the subendocardial layers of the myocardium and frequently engrafted on previously existing coronary artery disease.[4] This explanation is much less

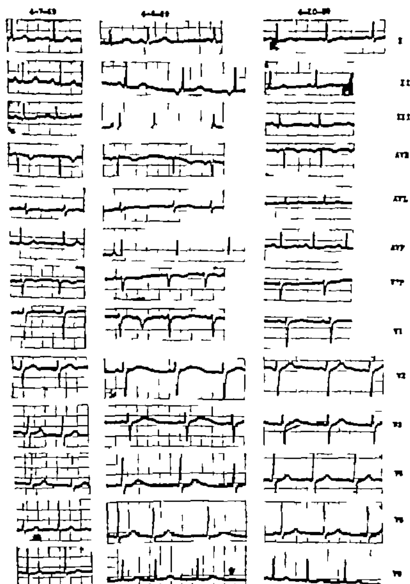


Fig. 1. Patient 19. The preoperative tracing of April 7, 1959, is normal. The second tracing was taken 2 hours after completion of the pneumoencephalogram. Note the marked prolongation of the Q-T interval (61.7 per cent), the inclusion of the U wave on the descending limb of the widened T wave, sinus arrhythmia, coronary sinus rhythm in Lead II, and an extrasystole in Lead V. The tracing of April 10 has returned to normal. The preoperative and postoperative serum electrolytes were normal.



Fig. 2. Patient 34. The preoperative electrocardiogram taken on May 5, 1960 is normal. On May 6, 2 hours after craniotomy for partial removal of left frontal lobe dermoid cyst, the electrocardiogram revealed marked diminution in the amplitude and notching of the T waves in the precordial lead. The tracing returned to normal by the fifth postoperative day. Preoperative and postoperative serum electrolytes were normal.

applicable to our material when we consider the age difference of our patients as compared with the usual population suffering from cerebrovascular accidents. More than half of our patients were below the age of 40. The great majority of our patients had no electrocardiographic or clinical evidence of heart disease. Furthermore, at autopsy the heart was reported to be normal in patients who showed electrocardiographic patterns suggestive of myocardial infarction in association with subarachnoid hemorrhage.

The third possible mechanism is that these changes in the electrocardiogram are a manifestation of altered cerebral function incident to the various neurosurgical procedures. The control exerted by the central nervous system on the various functions of the cardiovascular apparatus is indeed a very complex subject. Most of the studies in this area have been concerned mainly with stimulation of various cortical and subcortical areas and observations of readily detectable changes such as blood pressure and arrhythmias.[3,4] Of all the subcortical areas the hypothalamus has been studied most extensively, and it appears to have a definite relation to cardiac function. These studies, however, confirm

previous work with regard to striking alterations in rhythm and in the individual waves of the electrocardiogram during hypothalamic stimulation especially of the lateral and posterior portions. Some investigators have been able to reproduce cardiac changes which simulate the physiologic response to exercise by stimulation of various areas of the hypothalamus.[29] This work suggests that the myocardial responses may under certain circumstances be under neural control.

Other studies that may have some bearing on our results and observations relate to stimulation of the vagus nerve and its effects on the myocardium. There is some evidence in experimental animals that excessive vagal stimulation may in itself

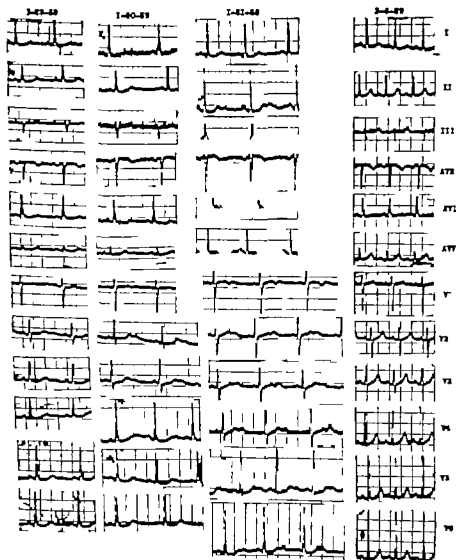


Fig. 3. Patient 6. The preoperative electrocardiogram and serum electrolytes (Jan. 29, 1959) were not remarkable. Three hours after ventriculography and craniotomy (Jan. 30) an electrocardiogram revealed prominence of the U waves and prolongation of the Q-T interval (39 per cent). Serum electrolytes were normal on this date. On the first postoperative day (Jan. 31) the prominence of the U w... as more striking. It merged with the descending limb of the T w... giving t... broad appearance and double peak. The tracing of Feb. 6 ... normal except for sinus tachycardia due to associated fever. Postoperative serum electrolytes were normal.

I II III VR VL VF V3R V1 V2 V3 V4 V5 V6

6/11/58 6/15/58 6/16/58 6/17/58 6/18/58 6/23/58 7/21/58

Fig. [illegible] (cont.) [illegible] June 11, 1958 [illegible] tracings [illegible] June 15 [illegible] taken [illegible] pneumoencephalogram [illegible] with the leading limb of the [illegible] and Q [illegible] (47 per cent) [illegible] of the [illegible] plus type. The following [illegible] (June 16) the [illegible] II, III [illegible] more [illegible] where the [illegible] in the right precordial leads [illegible] and more complete [illegible] with the [illegible] The Q [illegible] from [illegible] prolonged [illegible] the tracing of June 17 [illegible] June 18 the [illegible] in the right precordial leads [illegible] (June 21) the [illegible] inverted in [illegible] The tracing of July 11 [illegible] returned to normal 4 weeks after the last [illegible] procedure [illegible] normal.

lead to myocardial damage as demonstrated by the finding of infarcted areas congestion and hemorrhage at autopsy. These changes were more pronounced when the animal received eserine or acetylcholine or when vagal stimulation was performed in the unanesthetized state. Some of these animals were protected from arrhythmias and myocardial effects by pretreatment with atropine. Clinically it has been shown that serious cardiac arrhythmias can be prevented by increasing the depth of anesthesia during operation on the arterial system at the base of the brain. This protection occurs presumably by blocking damaging neurogenic stimuli to the heart. A state of excessive vagal stimulation has been implicated as the cause of electrocardiographic changes after pneumoencephalography and cranial trauma.

This short review seems to leave little doubt concerning the profound myocardial effects of autonomic dysfunctions under a variety of circumstances.

It is our contention then that most of the changes observed in the electrocardiograms in this group of patients represent an alteration in myocardial function brought about by a temporary state of excessive stimulation of the vagus and sympathetic nerves. Whether this excessive flow of reflexes created by irritation of various cerebral centers by the various neurosurgical procedures leads to biochemical anatomic or combined changes in the myocardium has not been elucidated to date.

Summary

The electrocardiographic alterations are reported in 37 patients who underwent various neurosurgical procedures. Striking changes were observed the chief of which consisted of alterations in the T wave prolongation of the Q T interval and increase in the amplitude of the U wave. Various considerations are discussed in an attempt to elucidate the mechanism of these findings. No significant alteration was noted in the serum electrolytes during the postoperative period. It is difficult to conceive that the electrocardiographic changes represent primary myocardial changes because the great majority of patients were without clinical evidence of cardiovascular disease and had an average age of 38.7 years. The electrocardiographic changes are most readily explained as being secondary to alterations in cerebral function after the various neurosurgical procedures.

We wish to thank Dr. Robert A. Groff Professor and Chairman of the Department of Neurosurgery of the Graduate Hospital and Graduate School of Medicine of the University of Pennsylvania for his cooperation and permission to investigate his patients during this study.

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Experimental and laboratory reports

Effects of selective myocardial stimulation or depression induced by intracoronary administration of drugs or by obstruction of major vessels. Studies with the dog ultralow frequency ballistocardiogram

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The chief difficulties of animal experimentation with the ballistocardiograph (BCG) have been overcome with the ultralow frequency technique,[1,2] so that additional experiments with this method give promise of advancing our knowledge in at least two directions. The first is that of special situations permitting a test of the method. As it has been used so far, the BCG records the forces which have their origin in the contraction of the heart. One hardly needs to be reminded that, although cardiac forces play a dominant role in the genesis of the force ballistocardiogram, the pressure in the vessels and their elasticity certainly affect the relation between cardiac forces and amplitude and form of the the record. We hoped to learn more about these noncardiac factors by studying the changes in the record caused by drugs which produce acute physiologic effects on the vessels alone or on the heart alone. For this purpose we employed a new technique of selective intra-arterial injection which could restrict the action of the drug to one or the other of these vascular compartments.

Our second aim was of more general interest. The results of the action of drugs and other agents on cardiac contractility are usually described in the well-known terms of stimulation and depression, terms which it must indeed be remembered are extremely inexact. Knowledge of the force ballistocardiogram and of certain aspects of the pulse now permits a more precise understanding of important aspects of the performance of the heart than had hitherto been available. We were interested, therefore, in attempting a more exact description of the changes in cardiac performance which are found in a few of the common physiologic stresses that can readily be set up in acute experiments on animals.

Methods

This study was performed on an ultralow frequency ballistocardiograph (ULF BCG) which was built especially for acute experiments with dogs. The instrument consisted of a rectangular frame (1.8 by 50 cm.) of hollow aluminum tubing (3.7 cm. in diameter) covered by lightweight canvas. This platform was suspended from the

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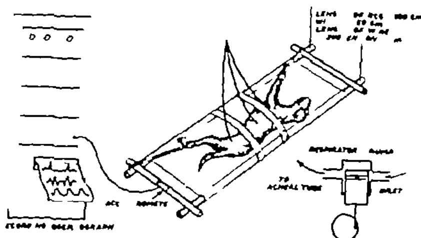


Fig. 1. Ultralow frequency dog ballistocardiograph (ULF BCG).

ceiling by means of 4 light steel cables which were about 3 meters in length. The natural frequency of the ULF BCG was 0.3 cycles per second. No external damping was used. Acceleration was transduced directly by means of a small (weight of 56 grams) variable capacitance accelerometer which was built for us by Dr. Walter J. Gamble. The weight of the unloaded platform was 3.25 kilograms (approximately one tenth of the average weight of the dogs used in the experiment). The signal from the accelerometer was fed into a D.C. amplifier and recorded on a 4 channel Sanborn oscillograph which allowed for concurrent monitoring of the ECG, systemic blood pressure, right or left atrial pressure, and respiration (Fig. 1).

Calibration of the instrument was obtained by the ratio $D/(L \times d)$ = sensitivity (expressed in terms of gravities per centimeter) in which D is displacement of the bed (centimeter), L is length of suspension (centimeter), and d is displacement of the pen on the paper.

Systemic arterial blood pressure was measured intraluminally from the femoral artery by means of a Lilly variable capacitance manometer or a Statham pressure transducer connected to a rigid polyethylene catheter, the signal of which was fed into a D.C. amplifier coupled to a multichannel Sanborn recording oscillograph. The recording system was accurately calibrated against a mercury manometer each time before use for linearity and accuracy of response.

The dogs used throughout the experiments were specially selected large mongrels or boxers, 30 to 35 kilograms in weight, which were in optimal nutritional condition and had good muscle tone. They were anesthetized with morphine (3 mg. per kilogram intramuscularly) and a combination of equal volumes of Dial and urethane in solution (100 and 400 mg. per milliliter, respectively), the dosage was 0.25 ml. per kilogram intravenously. One or both femoral arteries were cannulated for the recording of blood pressure or for insertion of catheter balloons, and one femoral vein was exposed and cannulated for injection of the drug. A plastic cannula was inserted routinely into the trachea.

Each dog was placed on his right side, his limbs were secured to the frame of the BCG by means of conventional leather straps, and wide (6 cm.) canvas belts were tightened across the chest and abdomen in order to obtain maximum coupling of the body to the bed. Spontaneous respiration was stopped by means of decamethonium bromide (0.2 mg. per kilogram intravenously) while an adequate respiratory exchange was maintained by means of an Ideal Starling pump connected to the tracheal cannula. The connections were such that no appreciable drag was exerted on the platform.

Insertion of modified catheter balloons into the pulmonary artery, aorta, and venae cavae (inferior and superior) was performed under fluoroscopic guidance. The position of the balloons was verified at

autopsy at the end of each experiment A rigid metallic catheter of a type previously described[7] was introduced through the left carotid artery into the circumflex segment or the anterior descending branch of the left coronary artery for direct intracardiac injection of the drug In two experiments both branches of the left coronary artery were catheterized at the same time All of these studies were conducted without opening the chest

Results and discussion

Certain theoretical concepts should be presented prior to setting forth the results of our experiments The views held by physicists for many years with regard to mechanical performance are applicable to the assessment of cardiac function When a force sets a body in motion as the energy applied by the heart sets the blood in motion an exact description of the effect produced requires three separate headings (1) effects related to displacement of blood or cardiac output (2) effects related to the velocity imparted to the blood including work in the Newtonian sense and friction (3) effects related to the acceleration of blood or cardiac force

Relationships have been demonstrated between these three aspects of cardiac performance and certain aspects of ordinary physiologic measurements Thus the BCG as we use it is a force recorder and both the depth of the I wave and the slope of the II J segment have proved to be quantitatively related to the force manifested by the accelerating blood at the onset of contraction[3] The slope of the advancing front of the pulse wave has also proved to be correlated with the acceleration of the ejected blood and conversely with cardiac force[3] the amplitude of this wave the pulse pressure with Newtonian work[4] the area under the systolic portion of the pulse wave (consideration is given to the blood pressure or the elasticity of the vessels) with cardiac output[3]

The regression equations used to derive a quantitative estimate of each of these three aspects of cardiac function were derived from experiments on human cadavers but they could not be applied to dogs without additional study Therefore no quantitative evaluations have been attempted in our studies with dogs Nevertheless we find it of great interest to trace the direction of the changes that occurred in these three aspects of cardiac function during the stimulation and depression of left ventricular contractility produced in our acute experiments with dog There is no reason to expect that these three aspects will always vary together and we were interested in observing whether the stresses of our experiments affected one variable more than another

Early in the experiment our attention

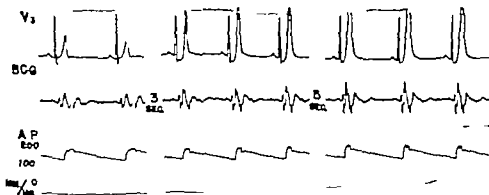


Fig 2 Response after the injection of sympathomimetic amine (epinephrine total dose of 5 µg) into the anterior descending branch of the left coronary artery Note the increase in amplitude of the I J wave and the change in slope Systolic blood pressure is practically unchanged except for the steeper slope of the pulse wave In all figures the paper speed was 50 mm per second The control record is always the first section on the left The markings at the bottom of each of the figures are in seconds

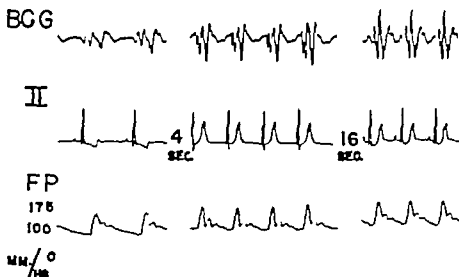


Fig. 3. Response after the injection of epinephrine (total dose of 5 μg) into the circumflex branch of the left coronary artery. Note the onset of nodal rhythm. The amplitude of the ballistocardiogram is increased but this improvement is not so conspicuous as that after the injection into the anterior descending branch (Fig. 1). A marked improvement appears after 16 seconds when the normal node again provides the pacemaker.

was attracted to changes in the J wave which seemed to be of peripheral rather than of cardiac origin. The J wave, according to Noordergraaf's quantitative theory of the ballistocardiogram, is chiefly the result of a footward acceleration of blood in the descending aorta and in the arteries of the legs. A much smaller factor is the deceleration of blood leaving the heart as it loses its headward velocity when reversing its direction of flow in the aortic arch and in the bifurcation of the pulmonary artery. Thus, the form and amplitude of the J wave depend on more than one factor. Of these, the most important factor is the acceleration with which the stroke volume is ejected by the heart. Other factors are the elasticity of the vessel walls and the blood pressure—the latter because vascular elasticity changes as intravascular pressure changes.

Cardiac stimulation. By injecting sympathomimetic amines (epinephrine, norepinephrine, and isoproterenol) which have powerful cardiac inotropic and chronotropic effects into the circumflex or anterior descending branch of the coronary artery, we tried to assess the effects of changes in left ventricular contractility accompanied by little or no peripheral change. It is thus possible to achieve a high concentration of the drug in selected areas of the cardiac musculature and to elicit local responses which are not obscured by systemic vascular reactions. Although it cannot be denied that reflex effects on the vessels might follow the changes induced in the muscle of the left ventricle, we believe that this technique is the nearest approach to a "pure" cardiac stimulatory situation that has been achieved in an intact animal and that the results are of interest for this reason.

In the majority of dogs the circumflex branch of the left coronary artery supplies blood to the atrioventricular node as well as to the septum and the posterior part of the left ventricle, whereas the anterior descending branch distributes blood to the anterior part of the left ventricular mass. The injection of a small dose of a sympathomimetic amine into the anterior descending branch of the left coronary artery is therefore *followed by an immediate* and marked increase in amplitude of the systolic complexes. As little as a total dose of 5 μg of epinephrine brings about a 100 per cent increase in the amplitude of the I-J wave, and its slope becomes very steep. Since the drug does not reach the conduction tissues of the heart, there is no chronotropic response; the ballistic effect is due

primarily to increased contractility of the muscle of the left ventricle with increased acceleration of the blood from the ventricle and a more complete and rapid ejection (Fig 2)

On the other hand the injection of a sympathomimetic amine into the circumflex branch of the left coronary artery because of its different distribution is attended by an altogether different response This is characterized by direct stimulation of the conduction tissue (positive bathmotropic and chronotropic effects) which leads to the transitory onset of a nodal rhythm (rythme nodal moyen) which consists of a succession of normal QRS-T complexes not preceded by a P wave[7] The atrioventricular node directly stimulated by the drug forms impulses at a faster rate than does the sinoatrial node and thus acts as a temporary pacemaker

Dissociation by interference is another interesting effect which often follows the intracoronary injection of sympathomimetic amines Under such circumstances one sees complete independence of the electrical and mechanical activity of the auricles and ventricles The atrioventricular node forms impulses at a higher frequency than does the sinoatrial node however a retrograde block prevents the atrioventricular impulses from reaching the auricles and perturbing the sinoatrial node which is discharging at a slower rate This phenomenon described by Wenckebach and Winterberger[8] in 1927 is well known in the clinic especially in patients who have received digitalis or atropine

Fig 3 shows the effects which followed the injection of epinephrine (total dose of 5 µg) into the circumflex branch of the left coronary artery The ECG shows that there was an immediate shift in the pacemaker with the induction of a nodal rhythm and a marked increase in heart rate The form of the ballistic record was profoundly changed There was a conspicuous increase in amplitude of all waves except H which became smaller and a deep notch appeared on the H I segment the area under the systolic pulse wave was almost unchanged and the blood pressure rose only a little but there was an increased steepness of slope in the ascending limb of the peripheral pulse wave As soon as normal atrioventricular conduction was re established with re emergence of the sinoatrial node as the pacemaker the form of the ballistic record returned to normal with an increased amplitude of all its systolic components This improvement is probably due to improved filling consequent to re-establishment of normal atrioventricular dynamics This is the type of response which usually attends the injection at this site of epinephrine norepinephrine or isoproterenol three sympathomimetic amines which possess to the highest degree the capacity for stimulating

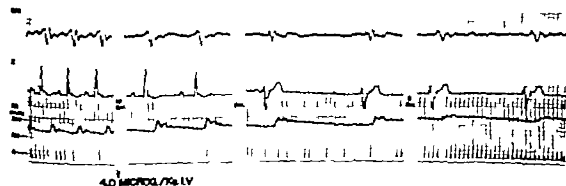


Fig 1 Response after the injection of a sympathomimetic amine having no inotropic or chronotropic action (methoxamine 4 µg per kilogram) After 10 seconds systemic blood pressure rises gradually whereas the heart rate slows A few seconds later systolic pressure is very high (about 200 mm Hg) and there is marked bradycardia due to baroceptor activation The ballistic tracing decreases in amplitude The rise in pressure and irregularities of intracardiac conduction Note the almost complete disappearance of the J wave in section of the tracing

the chronotropic and inotropic properties of the heart.

From these results we conclude that the chief effect of the stimulation was on the cardiac force, for the ballistocardiogram increased greatly in amplitude and the slopes of the I and the H-I waves increased as it did so. The slope of the pulse wave front was also steeper, whereas the changes in the pulse pressure and in the area under the pulse wave were far less evident. This suggests that in our experiments sympathomimetic amines administered by this method resulted in an increase in myocardial contractility rather than an increase in stroke volume.

This interpretation of the ballistic changes was further substantiated by the intracoronary administration of sympathomimetic amines in open-chest dogs in which a Walton strain gauge had been directly attached to the left ventricular muscle. The increase in amplitude of the systolic complex of the ballistocardiogram appeared in all cases to be directly correlated with the improvement of myocardial contractility consequent to the administration of those sympathomimetic amines which have a direct stimulatory effect on the release of energy by the ventricular muscle.

Peripheral vasoconstriction. In these experiments we sought to avoid the combination of peripheral and cardiac effects which are produced by most sympathomimetic amines when administered intravenously. We chose methoxamine (Vasoxyl), a sympathomimetic amine devoid of any positive cardiac inotropic or chronotropic actions, and injected it intravenously in doses of 4 mg. per kilogram three times in each of 15 animals. Whenever the drug was administered after atropine had been injected or cold had been used to block the vagus nerves, the type of response obtained was unaltered except for a less pronounced bradycardia.

Fig. 4 shows the results of a typical experiment. Ten seconds after the administration of the drug the heart rate slowed and the ballistocardiogram increased in amplitude. The pulse wave rose more steeply and the pulse pressure increased, although the rise in systolic and diastolic pressure was as yet small. This period of stimulation was transient; 3 seconds later evidence of heart block appeared in the ECG, and the heart rate became much lower. At this time the ballistocardiogram decreased in amplitude, the H-I slope was less steep, and the J wave amplitude was reduced. The pulse pressure was somewhat diminished, and the fall in blood pressure during diastole was extremely slow. Five seconds later these effects appeared to be exaggerated still more. The blood pressure was higher and the ballistocardiogram became distorted, with the J wave scarcely rising above the base line.

We interpreted these findings to mean that, confronted with increasing peripheral resistance, the heart rate became slower after an initial period of stimulation because of improved filling. The cardiac force, the work, and the output per beat were all increased during this brief period, although, judged on a per minute basis, this increase was not large. A few seconds later the high peripheral resistance after heart block had developed, indicated not only by the high blood pressure but also by the very slow fall of blood pressure during diastole, proved to be too much for the heart, and all aspects of its function were severely depressed.

These cardiac effects cannot be attributed to the direct action of methoxamine on the heart; rather, they must be thought of as consequences of the greatly increased resistance to ejection, or as secondary effects due to activation of carotid and aortic baroceptors by the rise of blood pressure, or as both. In this experiment an interesting distortion of the form of the ballistocardiogram developed: the J wave was greatly reduced and almost obliterated, while the preceding I wave was only slightly reduced in amplitude. We suggest the following explanation. *The I wave is to be attributed to the footward recoil of the body when blood is accelerated headward early in the ejection; the chief factor in the genesis of the J wave is the recoil of the body to the footward acceleration* of the long column of blood in the large thoracic and abdominal aorta and the arteries of the legs. The abnormality of form that is seen at the height of the action *of methoxamine, i.e., a disproportionate reduction of the J wave,* is what one would

expect if the mass of ejected blood after entering the aorta and pulmonary artery with little less than its usual acceleration were gradually damped and instead of immediately driving the long column of blood before it were accommodated in the aorta for a brief period by unusual stretching of the aortic wall Under such circumstances the long column of blood in the thoracic and abdominal aorta would be accelerated much more slowly than is normal and the forces which produce the J wave would be greatly reduced The extraordinarily low fall of femoral pressure during the long diastole indicates that peripheral resistance was greatly increased during the absence of the J wave Such abnormal resistance would certainly oppose and reduce the acceleration of the aortic and femoral blood This line of thought was further tested in the following experiments

Increased resistance from obstruction of the thoracic aorta Fig 5 shows the typical effect of the sudden inflation of a balloon mounted on the tip of a catheter in the thoracic aorta an experiment which was performed three times consecutively in 5 dogs The high aortic obstruction the completeness of which was indicated by immediate fall to zero of the femoral blood pressure was accompanied by a marked distortion of the J wave which was deeply split greatly reduced in amplitude and broadened Some reduction in the depth of the I wave and of the H I slope accompanied this change The form of the ballistocardiogram returned to normal as soon as the obstruction was removed

One must remember that a balloon inflated within a vessel effectively stops the flow of blood but it does not stop the transmission of forces Both ends of the air filled balloon are in contact with the blood in the aorta The rise in systolic blood pressure above the balloon dents its upper surface and increases the pressure inside the balloon This increased pressure distends the lower surface of the balloon thus imparting a force to the column of blood below The inflated balloon stops the flow of blood but the force passes through it although distorted by the physical properties of the air filled balloon which vary with its pressure One notes that the pulse is plainly visible in the tracing of the femoral pressure during the period of obstruction although the pressure below the balloon is so low that a considerable change in volume would be necessary to produce the small change in the recorded pressure

The notching in the J wave may well be a result of dissociation of the forces from the two sides of the heart those from the left side are delayed in time because the

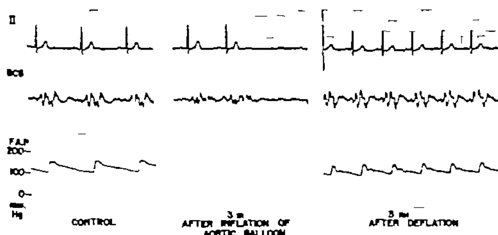


Fig 5 Typical effect of rapid obstruction of the thoracic aorta by means of the sudden inflation balloon mounted on the tip of catheter Note the reduction in amplitude of the ogram and the disappearance of the femoral pulse The ballistocardiogram re immediately after deflation of the balloon Three minutes later there over the control tracing

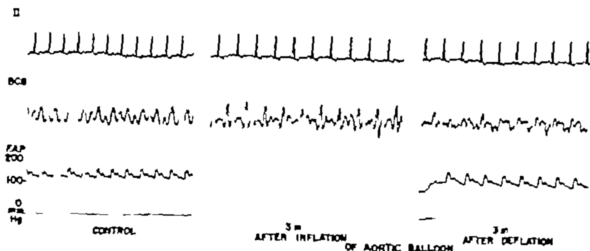


Fig 6 Effect of gradual obstruction of the thoracic aorta by means of the slow inflation of a balloon mounted on the tip of catheter *Femoral pulse pressure reduced to ripple Improvement of the ballistocardiogram* during inflation is probably the result of slowing of the heart rate Upon deflation of the balloon the ballistic tracing becomes distorted

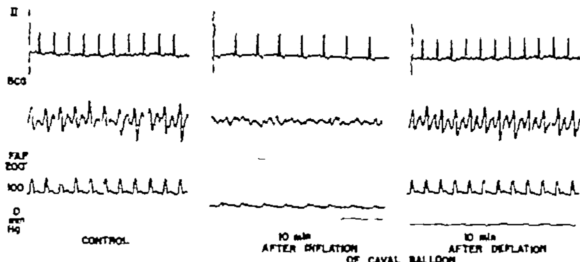


Fig 7 Effect of complete obstruction of the inferior vena cava by means of inflation of a catheter balloon Note the almost complete disappearance of II systolic complexes of the ballistocardiogram Femoral blood pressure is drastically reduced and pulse pressure very small Release of obstruction of the vena cava induces complete reversal of the effect

high resistance in the aorta has delayed ejection from the left ventricle There is no corresponding increase in resistance to right ventricular ejection Indeed the splitting of the J wave has been produced repeatedly in experiments on cadavers when systole has been simulated by asynchronous injection of the pulmonary artery before the aorta [8]

The broadening and slow descent of the J wave to the base line like the similar change described in aortic stenosis in man can be attributed to the diminished acceleration and deceleration of blood below the obstruction since it is the deceleration of blood units in the long aortic column which normally brings the J wave back to the base line at the usual time and which may continue to form the K wave

When we used a slight difference in technique we secured such a different result in another dog that we believe it should

be discussed (Fig 6) In this case a balloon was gradually inflated in the thoracic aorta. The physiologic state of the heart was very different in this experiment in the experiment illustrated in Fig 5 the heart rate was 70 beats per minute in this experiment 240 beats per minute. Such a rapid rate causes difficulty in interpreting the ballistocardiogram which should be explained here Inspection of the ballistocardiogram of the heart of a dog in good condition such as the ballistocardiogram reproduced in Fig 4 shows that the terminal complex the L M and N waves often relatively larger in dogs than in man occurs about 0 3 second after the peak of the R wave Obviously therefore when the cardiac cycle is as short as in the experiment illustrated the last waves of one complex are superimposed on the first waves of the following complex and distortion occurs This is the case in the control tracing in this experiment and exact interpretation of the record was difficult

Nevertheless interesting changes followed the slow inflation of the balloon in the thoracic aorta The heart rate slowed considerably (to about 180 beats per minute) and there was notable improvement in the ballistocardiogram which returned to normal After deflation of the balloon despite the normal blood pressure and pulse wave contour the ballistocardiogram became more abnormal than it had been before

This unexpected result may be compared to certain equally unexpected results in the clinic when a stress such as exercise has occasionally converted an abnormal ballistocardiogram into a normal one The interpretation of these phenomena has been as follows Cardiac stimulant drugs often convert an abnormal to a normal ballistocardiogram and this causes no surprise Exercise or any other type of stress which stimulates the heart by hormonal or nervous influences may produce a similar stimulating effect In our case the aortic obstruction proved to be a challenging stimulus to which the heart responded with an increased contractility and an improved performance

The rapid deterioration of cardiac function after the removal of the aortic obstruction is equally interesting and is consistent with the same concept The extreme abnormality which then developed suggests an incoordination of cardiac forces Since the pulse wave is not very different from that of the control period the disorganization of the ballistocardiogram can

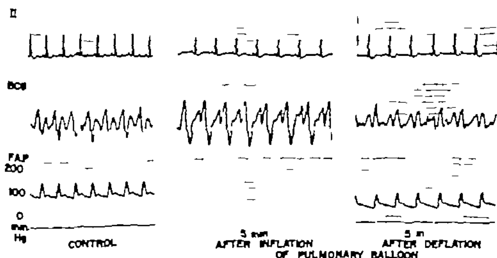


Fig 8 Typical result of obstruction of the main trunk of the pulmonary artery by means of catheter balloon The great increase in amplitude of the systolic complexes of the ballistocardiogram is unexpected result Acute cuspal insufficiency which allows backflow of blood into the venae cavae may account for this purpose

best be explained as asynchronous generation of forces from the two sides of the heart. This type of unpredictable response to various stresses is encountered quite often both in normal and pathologic conditions.

Hypotension produced by caval obstruction. A balloon was inflated in the inferior vena cava ten times in 4 dogs. Fig. 7 is an example of the result secured in this experiment. The systolic ballistic waves are easily seen in the control tracing, despite the fast heart rate which caused the Y wave to be superimposed on the H wave of the following beat.

The effect of obstruction of the vena cava was profound. The ballistocardiogram was greatly reduced in amplitude and so distorted that the waves could not be identified with confidence in many complexes. The H-I slope was almost flat in some complexes and greatly flattened in all; similarly, the pulse wave front had a very gradual rise. The pulse pressure fell to less than one fifth of its control value. The area under the systolic pulse wave was reduced to a small fraction of its former value.

Obviously the cardiac forces, work, and the stroke volume were greatly reduced. The lack of filling greatly handicapped the heart, and all aspects of its performance were depressed. The J wave was not increased, as after administration of vasodilating drugs, because despite the reduced peripheral resistance the stroke volume was so small and ejection was so slow that the column of blood in the thoracic and abdominal aorta was accelerated very feebly.

Cossio and co-workers[14] claimed that the impeded filling of the heart in open-chest dogs caused an increased amplitude of the ballistocardiogram, a view which was supported for a time by Thomas and co-workers.[15] On the basis of these results the theory that the ballistocardiogram had its origin chiefly in the movement of blood was challenged. Our results are similar to those of Honig and Tenney[8] and to those of Scarborough,[1] and so support the classic viewpoint. We have no intention of reviving the controversy here. It would seem, however, that experiments performed with improved techniques have not confirmed the results of Cossio and of Thomas and their associates.

Obstruction of the pulmonary artery. The inflation of a balloon in the pulmonary artery produced an effect which was totally unexpected. Fig. 8 shows a typical result. Similar results were secured four times in 2 dogs. Again, the interpretation of the control ballistocardiogram was made difficult by the rapid heart rate, but the distortion appeared to be slight. The great increase in amplitude of the ballistocardiogram after obstruction of the pulmonary artery was striking. This increase was due chiefly to greater depth of the K wave, but the slope of the H-I segment was also clearly increased during the pulmonary obstruction, even though the femoral blood pressure had fallen almost to zero and no pulse beat was visible.

For some time we were at a loss to explain this most unexpected result and indeed considered the explanation suggested by Cossio and associates, that movement of the heart itself might cause a ballistocardiogram even if no blood were ejected from the ventricle. One could not deny that under certain extreme circumstances this might be the case. Our results, however, are also in accord with another viewpoint which, consistent with other knowledge acquired recently, provides a more satisfactory explanation.

From McMichael and Shillingford's laboratory[16] have come a series of clinical observations which indicate that regurgitation through the tricuspid valve occurs frequently in clinical conditions; these investigators regard it as a compensatory mechanism which protects the right side of the heart against overdistention.

Also in experiments with the frog, an animal with a single ventricle, Klensch[17] found that experimental obstruction of the aorta leads to a ballistocardiogram of increased amplitude. Analyzing this unexpected result, which was so similar to ours, he observed that great distention of the heart had rendered the tricuspid valve incompetent, and that the heart was vigorously pumping blood back into the great veins at every systole. Thus the unexpected increase in the size of the ballistocardiogram could be attributed to this abnormal movement of blood.

Although the heart could not be observed in our closed-chest experiments it is well known that the right side of the heart dilates rapidly when confronted by a resistance too great for its strength and it seems inevitable that this happened in our experiments when the pulmonary artery was completely obstructed The best explanation for our finding seems to be similar to that given by Klensch the dilated heart because of the relative insufficiency of the tricuspid valve was vigorously taking blood from the veins and also pumping it back into them

However our attempts to obtain additional evidence without opening the chest were not altogether successful In flating a balloon in the inferior vena cava before inflating one in the pulmonary artery did not prevent the increase in ballistic amplitude the inability of an inflated balloon to stop the forces has already been discussed in this paper Also measurements of pressure gave little information because in a low pressure system such as the veins the relation of flow to pressure is far more remote than in the arteries

Summary

By means of the ultralow frequency technique excellent ballistocardiograms were secured in experiments with anesthetized dogs These records together with those for femoral blood pressure were employed to detect changes in cardiac function under various experimental conditions

To secure cardiac stimulation in as pure a form as possible drugs which stimulate cardiac action in doses too small to give generalized effects but large enough to produce localized responses were injected into both branches of the left coronary artery To secure peripheral constriction in as pure a form as possible drugs without direct cardiac action were injected intravenously

From the changes in contour of the ballistocardiogram and of the blood pressure curves the direction of the changes in cardiac force work and output was assessed Cardiac stimulation usually increases all of these aspects of cardiac performance depression usually decreases all of them Some aspects were often affected more than others

By means of balloons mounted on the tips of catheters the effects of obstruction of the aorta of the inferior vena cava and of the pulmonary artery were observed The latter gave a surprising result—a large increase in the size of the ballistocardiogram apparently a result of tricuspid regurgitation

By means of changes in peripheral resistance marked changes in the J wave of the ballistocardiogram were produced It seems evident that the amplitude of this wave can be altered by noncardiac as well as by cardiac factors The causes of other abnormalities of ballistic form produced experimentally in the dogs are discussed

We wish to acknowledge the generous assistance of Dr Isaac Starr Hartzell Professor of Therapeutic Research University of Pennsylvania School of Medicine Philadelphia Pa

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A scanner-computer for determining the volumes of cardiac chambers from cinefluorographic films

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Use of biplane cineroentgenographic and serial x ray techniques for measurement of the volume of various cardiac chambers has been shown to be reasonably reliable [1] The chief objection in practice is the tediousness of the various tracing operations and of the laborious calculations that are involved in some of the methods In order to overcome this objection consideration was given to the development of mechanical and electronic adjuncts to facilitate tracing chamber boundaries and to carry out the necessary calculations

The method for which the instruments to be described were developed has been published in detail In the case of the left ventricle it requires the tracing of two simultaneously filmed images (35 mm film) recorded at a rate of 30 per second Measurements of corresponding diameters of the two images are then made at 1 mm intervals from top to bottom and the values are inserted into the usual equation for the area of an ellipse (or circle)

$$A = \pi \frac{d}{2} \frac{d}{2}$$

where d_1 is diameter obtained from one ventricular image and d is the corresponding diameter from the other simultaneously recorded image Since diameters are measured at 1 mm intervals the area in square millimeters is numerically identical with the volume of a section of the ventricular cavity that is 1 mm thick (Fig 1) Total ventricular volume is merely the sum of all the sectional volumes

In practice it is necessary to trace up to 80 pairs of images for each run (4 to 8 cardiac cycles) Usually from 50 to 70 diameters are measured on each pair of images necessitating a vast number of separate multiplication and summing oper

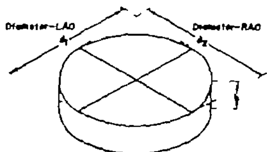


Fig 1 Section of cylinder showing the axes (diameters) used in calculating volume The total volume of the cylinder (or ventricle) is the sum of those of the individual sections

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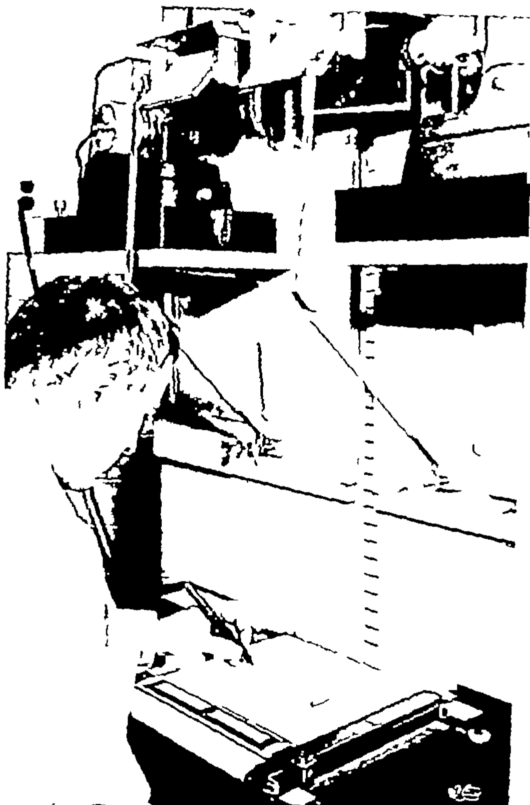


Fig 2 Operator tracing ventricular contour from one of two simultaneously filmed views of the heart The corresponding frame in the other view has already been traced and is seen to the operator's right Active areas (A and P) are indicated by the white rectangles on the ruler at the edge of the platform nearest the operator Operational marks can be seen near the edges of the paper

ations. It is not unusual for the calculations for a single run to occupy 3 workers for 2 to 3 weeks.

It was originally hoped that the entire measurement and calculation procedure could be done electronically. It was not feasible, however, to entrust tracing of chamber boundaries to an electronic scanner or densitometric device. This operation for many reasons requires judgment and constant comparison of sequential images. For this reason, tracing is done from 35 mm original films, using a 16 mm reduction print of the same original to establish the location of valve planes and other details. The process, with experience and the help of mechanical aids, goes rapidly.

Tracing equipment

Two 35 mm still projectors are mounted on an upright standard as shown in Fig. 2. Images of individual frames are projected by use of appropriately placed front-surfaced mirrors onto a tracing platform in such a way that chamber images are relatively undistorted. The tracing platform is designed to receive slotted roller paper 27 cm wide on which corresponding chamber images can be very precisely located and traced (Fig. 2). Owing to the design of the scanner (see below), images must be traced firmly and definitely in black ink. Small operational marks are appropriately placed in order to instruct the scanner to commence or to cease measurement (Figs. 2 and 3). In the event that images do not fit easily into X or Y areas (Fig. 3), they can be reduced one half and the final calculation corrected accordingly in the computer. Conversely, if images are too small to be handled accurately, their size can be doubled and the fact taken into account in final calculations.

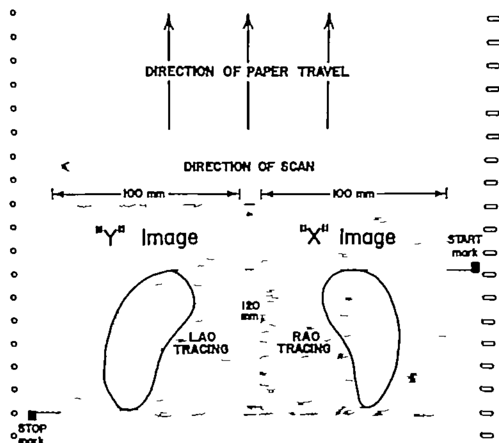


Fig. 3. Section of slotted paper bearing 2 ventricular tracings. Locations of operational (*start, stop*) marks and the active areas (X and Y) learly shown.

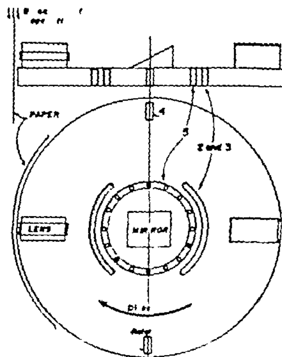


Fig 4 Diagram of scanning disk viewed from above and in cross section Areas that are filled in with parallel lines represent counterbalancing weights and slots See text for description of purposes of slots numbered *1* to *5*

ameter first in X area then in Y area Slot *4* has to do with the mechanism for instructing the machine to print a finished calculation The ring of circular slots is concerned with holding the counting rate at precisely 1 65 machine units per millimeter The counting is accomplished by a pulse generator situated between the photomultiplier tube and the computer

The computer

Fig 4 shows the computer (to the left of the scanner) with logic multiplier accumulator and printing compartments arranged in that order from above downward under the control panel and oscilloscope

The *multiplier* accepts impulses from the photomultiplier tube in the scanner unit and multiplies X and Y diameters The result is transmitted to the accumulator which sums and stores the results After the final scan the stop mark on the slotted paper signals the logic compartment which in turn activates the printer Scanning errors are also noted by the machine and summed on the final printed tape The scanning operation can be easily followed on the oscilloscope screen

Accuracy of operation

Theoretically the only errors possible in the system are those which result from faulty scanning which in turn results from improper tracing extraneous marks on the paper or faulty placement of operational marks The possibility of error due to faulty synchronization (and change in counting rate) is rendered very remote by the *inclusion of a device to maintain* a fixed relation between the pulse generator and the rate at which the disk revolves (which is synonymous with the rate of scanning)

Tests of accuracy in which spheres and other objects are used suggest that the machine does the job most reliably For spheres the percentage of error attributable to the machine is slightly over 1 per cent (Table I) For a cylinder with a conical tip which was rotated before the cinecameras (Table II) most of the error is introduced by the method itself and not by the machine Both the laborious Simpson's rule technique and the calculation from the same tracings by the scanner computer overestimate the true volume of the object (by as much as 12 per cent) Comparison of the two techniques of measurement however shows that the machine is at least as good as human operators and much faster Much the same can be said when a model of the left ventricular cavity is tested

Table I Comparison of calculated (actual) volumes of spheres and their volumes as determined by cinefluorography and use of the scanner computer

Radius (cm)	*Calculated volume (ml)*	*Computer volume (ml)*	*Difference (per cent)*
1 5	14 12	14	−0 86
2 0	33 51	33	−1 54
2 5	65 45	64	−2 76
3 0	113 10	111	−0 89
3 5	179 59	178	−1 16

*The instrument tends to underestimate volume slightly

Table II Results using models (above) and casts (below) of left ventricular cavity

	Position	Actual	Volume (ml) Simpson's rule	Scanner computer	Difference (per cent) (Simpson rule compared with scanner computer)
Cylinder with conical tip	1		181 0	18	+0 54
	2		19 0	201	+1 99
	3	178 5	205 2	208	+1 34
	4		20	201	−0 84
	5		196 4	194	−1 1
Plaster model of ventricular cavity	1		2 9	269	−3 1
	2	2 4	312	315	+0 96
	3		295	303	+ 1

The cylinder ... revolving ... photographed and positions 1 ... 5 represent successive film frames. The plaster model ... cavity was photographed in three different positions ... used ...

Application

The scanner-computer has been used for calculation of left ventricular volumes in dogs and in man. It also is currently being used to calculate change in volume in aortic aneurysms, giant left atria and other more-or-less spherical or cylindrical structures. Its chief value is that by reducing the time needed and the tedium of measurements made on serial x-ray films or on cineangiocardiographic records it makes a contribution to the use of x-ray techniques for quantitative measurements of circulatory function.

The scanner-computer was designed and built by the National Data Processing Company, 4 03 Ross Avenue, Dallas, Tex.

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Movements of the heart during ejection

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Previous reports have dealt with cardiac motions which occur during the pre-ejection phase of systole and during ventricular relaxation. The purpose of the present communication is to describe the movements which occur during ejection.

Methods and subjects

The techniques employed were identical with those described in the previous studies. The pressure curves from the four cardiac chambers, from the aorta, and from the pulmonary artery of dogs were differentiated[4] and the resulting pressure velocity traces were studied in relation to each other and in relation to the precordial movements of normal human subjects. Since each change in slope in the conventional pressure records is reflected in the first derivative by a change in the magnitude of the corresponding deflection, the latter provides more information in regard to the time course of the changes in pressure for comparison with the complex precordial traces from human subjects.

The term *velocity record*, as used in this communication, refers to the first derivative of the pressure curve. These derivative records were recorded at convenient amplitudes and do not represent absolute values.

The precordial records analyzed were the same as those utilized in the previous studies of isometric contraction and of relaxation. Although tracings were made on 50 normal persons from the several V points of the precordium, records from multiple intercostal spaces in a single vertical line were obtained in only 10 subjects. The discussion to follow will deal only with the latter group. The findings in the other 40 subjects were essentially the same.

All precordial tracings were made with the subjects holding the breath at the end of normal expiration. Electrocardiograms (Lead I or II) and carotid pulse tracings (glycerine capsule) were used as timing references.

The terms used in the present report correspond to those in preceding studies. Thus K_1, K_2, K, and K_4 refer to kinetocardiographic tracings as obtained from the corresponding V lines. The second numeral designates the intercostal space from which the tracing was made. Therefore the term K_1 indicates a tracing taken from the right second intercostal space, whereas K_{55} refers to a record obtained from the left anterior axillary line in the fifth intercostal space, etc. Tracings from the suprasternal notch are indicated as K, whereas the right and left epigastric records are designated K and K, respectively.

In the case of records from the right and

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left parasternal and from the left midclavicular lines the pickup device was directed in an anterior posterior direction and therefore downstrokes and upstrokes denote posterior and anterior motion respectively. The anterior axillary (K_4) traces were also taken perpendicularly to the chest wall and upstrokes in these may mean either forward or leftward movements. However in the records from the other regions the oblique angle of the recording device was such that upstrokes indicate either headward or forward movement (K or suprasternal notch) and either footward or forward motion (K and K right and left epigastric regions).

Results

A Pressure velocity curves of dogs during ejection. The data are summarized in Table I and illustrated in Figs. 1 and 2.

1 THE VENTRICLES AND GREAT ARTERIES. The onset of ventricular ejection was characterized by an abrupt decline in the ventricular velocity trace which occurred simultaneously with the rise in aortic or pulmonic pressure. The velocity records from the vessels soon reached their peaks and began to decline. A small upstroke (Fig 1 *second arrow*) then occurred in the aortic and less commonly in the pulmonary arterial traces. This was sometimes associated with a less prominent upstroke in the ventricular derivative (Table I). The velocity traces then exhibited further reduction even though the absolute pressures were still increasing rapidly.

As rapid ejection ended the usual "shoulder" in the ventricular and arterial pressure curves was associated with a continuing decline in their derivatives. The small upstrokes in the conventional pressure records at the onset of the phase of reduced ejection were more clearly seen in the velocity records (Fig 1 *third arrow*). This phenomenon was observed in every animal and was noted to occur slightly earlier in the ventricular than in the aortic traces.

Throughout the remainder of ejection the velocity records tended to maintain a slow decline and the aortic curves often exhibited what appeared to be either artifacts or harmonic vibrations of the elastic aortic wall.

Comment. During rapid ejection the actual ventricular pressures continue to rise. However and possibly because the opening of the semilunar valves causes sudden enlargement of the total volume in direct communication with the cavities the *rate of rise* decreases abruptly and the ventricular velocity traces exhibit sharp decline as the arterial upstroke begins. The arterial derivative soon reaches its peak and the velocity of rise then diminishes even though the undifferentiated records show that the absolute pressure is still increasing rapidly.

The second small rise in the aortic velocity trace would appear to be of vascular origin because it tended to precede slightly the smaller and less constant increase in the ventricular trace. This deflection is possibly due to elastic recoil of the aortic wall after its sudden distention. As might be expected this deflection was seen less frequently in the records from the more distensible pulmonary artery. The possibility that it is of artifactual nature cannot be excluded.

The small upstroke which occurred regularly in both the ventricular and the arterial traces at the onset of reduced ejection would seem to be of ventricular origin because it appeared slightly earlier in the records from the cavities than in those from the vessel. Its mechanism will be considered in the later discussion.

2 THE ATRIAL VELOCITY RECORDS. The data are shown in Table I and Fig 2. During the early part of ejection each animal displayed two abrupt upstrokes in the derivative traces of the two atrial pressures. All dogs likewise displayed two sharp downstrokes in the atrial velocity records. In the latter part of ejection a gradual rise was noted. These various events tended to occur slightly earlier in the right than in the left atrium.

Comment. These several phenomena may be explained as follows. The abrupt upstrokes in the atrial derivatives are probably to be ascribed to headward ballooning of the closed atrioventricular valves consequent to the high intraventricular pressures. The sharp downstrokes in the velocity record indicate either actual decline or decrease in the rate of rise in pressure in the atria. Such ef-

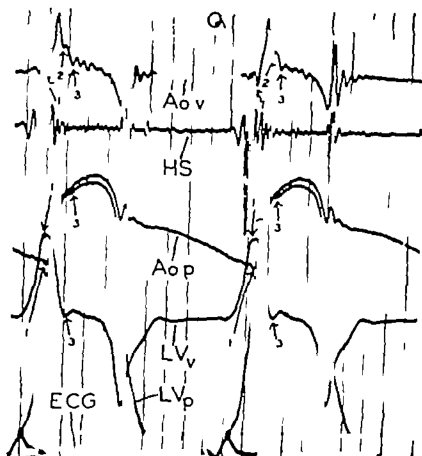


Fig. 1. The traces of left ventricular (*LV*) and aortic (*Ao*) pressure (*p*) and of the first time derivative of pressure or pressure velocity (*v*) of a dog are shown during two successive cardiac cycles. The ECG and heart sounds (*HS*) are also depicted. Time lines 0.04 second. Paper speed 100 mm. per second. *1*. The onset of left ventricular ejection is shown by the abrupt rise in the aortic pressure and velocity traces and by the sharp decline in the left ventricular velocity record (*first arrow*). This change is not clearly seen in the undifferentiated LV curve. *2*. The aortic velocity trace reaches its peak about 0.02 second after ejection begins and then declines rapidly. This decline is not smooth but is interrupted by a small upstroke (*second arrow*) which in other animals was sometimes reflected in the ventricular records (Table I). It is possibly due to elastic rebound of the aorta but may represent an artifact. *3*. About 0.05 second after the onset of LV ejection the now declining aortic and LV velocity traces exhibit an increase in the rate of rise in pressure (*third arrow*). This is more apparent in the ventricular than in the aortic record and is present although less obvious in the undifferentiated traces. The mechanism of the second rise in pressure is discussed in the text. The subsequent rapid deflections in the aortic velocity trace are not seen in the ventricular record and are probably to be ascribed either to vibration of the aortic wall or to artifact.

point toward descent of the atrial floor. This might be due either to additional shortening of the papillary muscles or to a further movement (in addition to that which occurs during isometric contraction) of the atrioventricular rings toward the apex. The data supply no evidence as to which of these motions preceded the other.

The slow rise in the atrial pressures during late ejection (*V wave*) is probably due to filling of these chambers. There is ample evidence that this occurs during ventricular ejection and it is naturally facilitated by the descent of the closed atrioventricular cusps.

3. RECIPROCAL CHANGES IN THE VENTRICULAR PRESSURE VELOCITIES. It has been shown that during isometric contraction[1]

and during relaxation the two ventricular pressure derivatives often display abrupt changes in opposite directions Since such changes are probably guides to the movements of the interventricular septum the velocity tracings recorded simultaneously from the two ventricles during ejection were scrutinized for reciprocal deflections No consistent tendency toward such was encountered Such displacement of the interventricular septum as may occur in dogs during ejection would appear to be masked by the other motions which have been considered

B Precordial movements during ejection The findings are summarized in Tables II III and IV and in Fig 3 and are illustrated in Figs 4 and 5

I SIZE OF THE LARGER MOTIONS The total amplitude of the precordial excursion

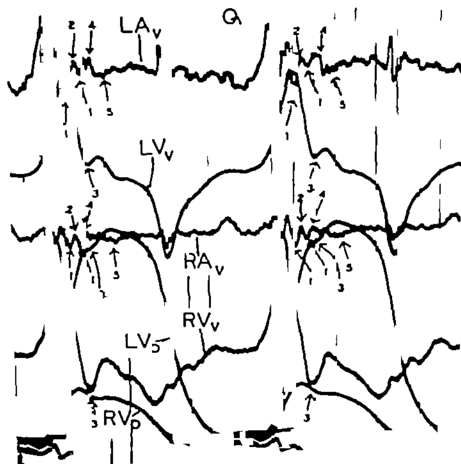


Fig 2 Conventional (*p*) and velocity ( ) pressure traces from the four cardiac chambers of dog are shown during two successive cardiac cycles beginning and ending at the onset of ventricular excitation Time lines 0 04 second Paper speed 200 mm per second The onset of ejection of each ventricle is shown by the large downstroke in the respective velocity record Shortly after the beginning of left ventricular ejection each atrial velocity trace displays two abrupt upstrokes (*1*) separated and followed by downstrokes (*2* and *4*) These might conceivably be artifacts but the close correspondence to the precordial deflections in record from human subjects (*see text*) and the constancy of occurrence of one or more of these deflections in the record from different dogs at the same time in the cycle make this unlikely The upstrokes are attributed to head and bulge of the atrioventricular cusps and the downstrokes to further descent of the ring and/or additional shortening of the papillary muscles The small slow upstroke (*5*) which begins some what later is probably due to atrial filling As the phase of reduced ejection begins each ventricular velocity trace exhibits an upstroke (*3*) indicating increased rate of rise us pressure which may also be seen in the undifferentiated pressure traces See Fig 1 and text

Table I Summary of changes in pressure velocity in the cardiac chambers and great arteries of

Motion	Left ventricle and aorta		Right ventricle and pulmonary artery		Interpretation
	Present in	Mean time (sec)	Present	Mean time (sec)	
Arteries ↗ Ventricles ↘	All	0	All	Variable†	Onset of ejection
Arteries ↘	All	0 016	All	023	Peak velocity of rise in pressure
Arteries ↗ Ventricles ↗	All 5 of 6	0 021 0 024	2 of 5 2 of 5	025 025	Elastic rebound or artifact
Ventricles ↗ Arteries ↗	All All	0 036 0 044	All All	044 047	Laplace effect? (see text)

Time aft[illegible] set of l[illegible] ventricular eject on
†Right ventricular ejection [illegible] left ventricular eject
‡Un[illegible] [illegible] of papillary muscles pull of papillary muscle [illegible] responsible [illegible] movement

Table II Mean times and amplitudes of larger movements during rapid ejection

Movement		Right parasternal		Left parasternal	
		Upper (Av[illegible])	Lower (A[illegible])	Upper (Av m)	Lower (Av m)
Total amplitude of trace (mm)		15 4	22 8	17 5	27 8
Large outward motion	Time (sec after Q)	Absent	Absent	0 110	0 105
	Size (mm)	—	—	2 2	6 0
Large inward motion	Time (sec after Q)	0 111	0 115	0 143	0 136
	Size (mm)	11 6	16 6	7 2	20 2

and the size of the major deflections are shown as averages in Table II It will be seen that the degree of excursion was greatest in the lower precordium and tended to be larger in the left parasternal than in the other areas

II GENERAL CONFIGURATION OF RECORDS The traces from the lower left precordial regions resembled ventricular volume curves in most respects Records from the right parasternal areas were rather like atrial pressure curves Deflections from the suprasternal notch were similar to those of an arterial pulse These several configurations are illustrated in Fig 4

A considerable variability in general contour was encountered in the traces from the upper left intercostal spaces In most

dogs during ejection

Motion	Atria: Left: Present	Atria: Left: Mean time (sec)	Atria: Right: Present	Atria: Right: Mean time (sec)	Interpretation
First ↗	All	004	All	0 00 before	Bulge of A V cusps
First ↓	All	016	All	0 008	Descent of A V cusps
Second	All	0??	All	0 025	Bulge of A V cusps
Second ↓	All	038	All	0 032	Descent of A V cusps
Late slow ↗	All	073	All	0 064	Atrial filling

Mid clavicular: Upper (K)	Mid clavicular: Lower (K)	Anterior axillary: Upper (K)	Anterior axillary: Lower (K)	Epigastric (K K)	Suprasternal (K)
14 3	20 9	12 7	10 2	19 2	13 1
0 111	0 104	0 118	0 110	See Table III	0 116
4 6	9 3	5 2	4 9	—	7 6
0 156	0 145	Variable (0 18–0 32)	Variable (0 15–0 25)	0 139	Absent
6 1	14 1	Variable	Variable	15 0	Absent

instances records from the second intercostal space in the anterior axillary line (K) were of the arterial type (Fig 4 F) This configuration was found less frequently in the K region and was occasionally seen in the upper (second and third) intercostal spaces in the mid clavicular and left parasternal lines More commonly the records from the latter areas were of a mixed type they had some of the features of arterial pulse tracings and resembled ventricular volume curves in other respects

III SPECIFIC DEFLECTIONS The several movements which were commonly observed during the period between 0 08 and 0 105 second after the onset of the QR e between the beginning of right an

Table III Precordial motions during period from onset of left ventricular ejection to start of

Motion	Frequency of occurrence	Time of onset after Q (sec)
Large outward of left lower precordial area	Lower k Constant	0 104 (0 09–0 12)
	Lower k Constant	0 110 (0 08–0 14)
	Lower k (29 of 30)	0 105 (0 08–0 12)
	k (8 of 10)	0 103 (0 09–0 12)
k Large inward	k Constant	0 112 (0 085–0 14)
Outward of suprasternal and upper precordial area	Suprasternal Constant	0 116 (0 10–0 14)
	Upper k (19 of 20)	0 118 (0 10–0 14)
	Upper k_4 (19 of 20)	0 111 (0 09 0 13)
	Upper k (17 of 20)	0 110 (0 085–0 13)

*S of m on of t th total ampl tud (t) ecw d br wt l h st accurred

Table IV Systolic movements of precordium in relation to carotid pulse

Motion		Time of onset (sec)		Frequency curson area
		After Q	Carotid	
During rapid carotid upstroke	Main left precordial and epigastric downstroke	0 13 ± 0 03	0 02 ± 0 01 after CU	Constant t lower k and k_4 ariable t k
	Small right parasternal upstroke	0 18 ± 0 04	0 06 ± 0 03 after CU	Constant k high Frequent k low Absent elsewhere
During reduced ejection	General outward motion	0 215 ± 0 035	0 09 ± 0 0 after CU	k constant k Almost constant Others Frequent
	Late inward motions	0 26 ± 0 05	0 15 ± 0 05 before CIN	k constant in one or more areas k_E Almost constant
	Inward motion of supracardiac area	Variable	Variable	k Constant k_4 Usual k_{44} et al Occasional

CU Onset of carotid upstroke. CIN Carotid incisural notch k_E Epigastric area k Trace from supra sternal notch

carotid upstroke

Amplitude		Remarks	Tentative interpretation
Absolute	Relative		
Large	Cre test at h₄₄ (pe) h₄₄ h₄₄	Abs t at h	Forward leftw rd foot and r d of left entrick
Large t lower h₄	Largest pper h	h h h₄ Ir ous outward motion cont ues	Decre se n olume due to ejection of both entricles
Largest t suprasternal and h areas		Present t h in ly one subject	E pansion of great essels and/or bulge of mitral cu ps

Relative size in different areas	Remark	Tentative interpretation
Low > high h > h₄ hₚ Large	Roughly parallel t stroke olume	Volume hange in ejection
h₄ High > low	Often fused with next and larger outward motion	B lge of tricuspid al t trium
h₄ High > low h₄ Low > high	About 0 01 sec after end of rapid ejection Often less fourth than in higher or lower intercostal spaces	Atrial filling (h) also descent of inferior border (h) Descent of mitral leaflets
Low > high	Variable small deflections t h h₄ h	Volume change in jection Terminal shortening of LV with backward headward pull and decreased base pex length
Low Absent	Large relativ size	Vascular runoff (? also pull on semilunar rings?)

LV Left ricle

left ventricular ejection respectively have been discussed in the previous report which dealt with the pre ejection phase of systole[1] The motions seen during the period when both ventricles are ejecting are summarized in Tables III and IV They may be subdivided according to their relation to the carotid upstroke

A *Motions between the onset of left ventricular ejection and the start of the carotid upstroke* (*Table III*)

1 *The main outward motion in the lower left precordial region* Approximately 0 105 second after the beginning of the QRS an outward deflection was observed in the lower K_4 K and K_6 intercostal spaces (Figs 3 *A* 4 and 5) This movement was usually largest in the region of the apex (Table II) as would be expected since it corresponds to the normal apex tap It appeared to occur about 0 005 second later in the anterior axillary line than in the lower precordial areas Aside from deflections due to the ejection downstroke and to filling this is often the largest movement in the normal precordial trace

The relationship in time of this motion to the ballistocardiogram and to the carotid upstroke was of some interest In the older subjects it preceded the latter by approximately 0 015 second whereas in the younger group this motion occurred about 0 025 second before the start of the carotid upstroke In a given person this motion corresponded closely to the second portion of the biphasic *H I* downstroke of the low frequency acceleration ballistocardiogram

This sudden outward motion is reduced in amplitude in many patients with cardiac disease although those with left ventricular hypertrophy commonly display a larger more gradual and longer sustained deflection which starts earlier in the cycle

This deflection appears to correspond to the onset of left ventricular ejection in the dogs as shown by the sharp rise in the aortic pressure and velocity traces and the simultaneous decrease in the left ventricular velocity record (Figs 1 and 2)

Comment In a previous publication[4] evidence was presented for the view that this abrupt and large outward motion of the precordium represents recoil as left ventricular ejection occurs The shorter duration between the onset of this motion and the beginning of the carotid upstroke in the older subjects is attributed to more rigid arteries and shorter pulse wave transmission time

2 *The largest right parasternal inward motion* At 0 112 ± 0 025 second after Q a large downstroke occurred (Figs 3 *B* and 4 *A*) The absolute amplitude of this movement was greater in the lower (K_{R4} and K_5) than in the upper (K_{R2} and K) intercostal spaces However the amplitude relative to the total excursion of the trace was about the same (Table II)

Comment This deflection occurs at a time when both ventricles are ejecting rapidly and is ascribed to the volume change of ejection It corresponds well in time to the first large downstroke observed in the atrial pressure velocity trace of dogs (Fig 2) These observations constitute evidence in support of the concept[4] that descent of the tricuspid leaflets is of major importance in the mechanics of right ventricular ejection It is uncertain whether this motion is due to additional shortening of the papillary muscles or of the superficial fibers with a downward pull on the tricuspid annulus

3 *Outward motion in the suprasternal and upper precordial areas* At 0 10 to 0 14 second after Q (average 0 117) the suprasternal and the upper left axillary traces exhibited outward excursion (Figs 3 *C* 4 *E* and *F* and 5 *E*) The upper K_3 and K_4 areas sometimes displayed outward movements which began slightly earlier (Table III) All of these deflections occurred a few thousandths of a second after the larger left lower precordial outward motion which has already been considered

Comment These movements began about 0 01 second before the start of the carotid upstroke In the suprasternal area this motion was the beginning of the pulse wave contour This observation suggests that the deflection is related to the systolic expansion of the great vessels However the left atrial velocity records of the dogs (Fig 2) exhibited at this time a sharp upstroke which indicated headward bulge of the closed mitral leaflets Possibly both of these factors contributed to the outward motion of the upper precordial region as observed in man

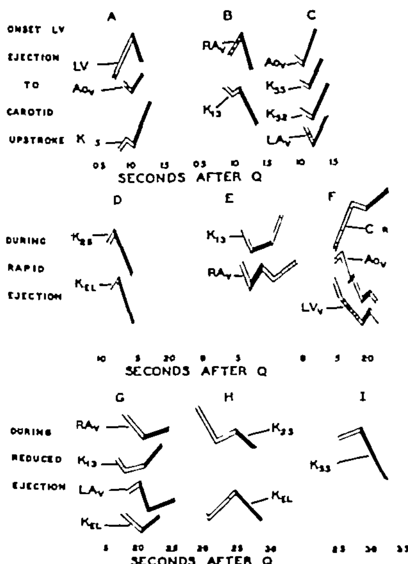


Fig 3 Diagram of cardiac motion during ejection The actual times of the pressure velocity ( ) deflections of the dogs have been altered to correspond to the same heart rate that was present in human precordial records (K) A Onset of left ventricular ejection is indicated by abrupt respectively fall and rise in left ventricular and aortic derivatives of the dog and by quick outward recoil in the region of the apex B Large inward motion in the right parasternal region (K) apparently corresponds to sharp descent of right atrial floor C Upstrokes in the suprasternal notch (K) and in the second intercostal space in the left anterior axillary line (K_{32}) follow the aortic upstroke (Aov) by about 0 01 sec which approximates transmission time of the pulse to the aortic arch and subclavian artery The possibility that headward bulging of the mitral cusps which is regularly seen in the left atrial traces of the dogs (LA) contributes to these outward motions of the supracardiac area cannot be excluded Motions A B and C are almost simultaneous D Large downstrokes over the lower precordium and in the epigastrium represent change in volume Analogues in the derivatives of the dog pressure traces occur earlier (A) E Upstrokes in the right atrial velocity curve and in the upper right parasternal area (K) are both ascribed to bulge of the tricuspid leaflets into the right atrium F The aortic pressure velocity curve displays small upstroke which is probably due to elastic rebound and which is sometimes associated with a change in slope in the ventricular velocity record Just after the end of the rapid ejection these two records and the human carotid (Car) trace display upstrokes These are possibly related to the effect of reduced volume on pressure (see Discussion) G Two different motions are illustrated The outward motion in the left epigastric area (K) coupled with abrupt decline in the left atrial velocity record points toward a change in shape in the left ventricle due to descent of the mitral leaflets The rise in the two atrial velocity curves associated with generalized outward motion of the precordium greatest in the area of the right atrium (K) suggests that the atria are filling more rapidly than the ventricles are emptying H The terminal inward precordial motions are ascribed to backward and headward motion of the heart borders No clear analogues were encountered in the pressure derivative traces of the dog I The last motion observed in the precordial records was large downstroke in the suprasternal traces This is ascribed to runoff from the aorta

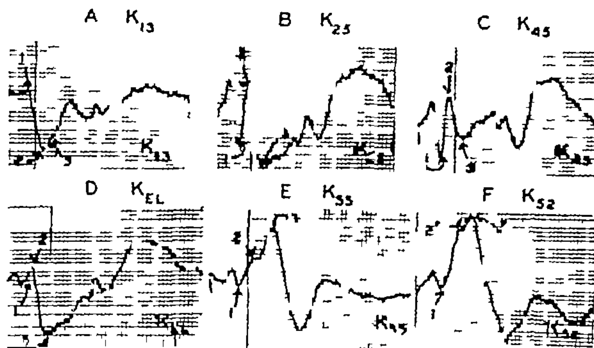


Fig 4 D G a normal 6- ear-old man Time lines 0 0 second The traces begin nd end t the onset of the QRS Note the resemblance of the different records to entricular olume (B C D) arterial pulse (E F) and trial pressure (1) traces As left entricular ejection begins three phenomena are noted (1) A large recoil upstroke is seen over the lower left precordium (f st arrow B and C) nd in the epiga trium (first arro. D) 1 B this upstroke is preceded by much smaller one due to right entricular recoil (2) The right parasternal record (4) di play prominent downstroke (f st arrow) attributed t descent of the tricuspid leaflets (3) The suprasternal (E) and high left axillary (F) records exhibit large pstrokes hich are attributed t expan sion of the aorta and the left subcla ian artery respectively During the early part of rapid jection the main inward motion of the left precordial (B and C second arrow) and of the epigastric (D second row) regions occurs A little later the small right para ternal upstroke (1 second arrow) ascribed to bulge of the tricuspid leaflets seen As reduced ejection begins large (A th rd arro.) or small (B and C third row) outward motion occurs This is attributed to rapid filling of the posteriorly tuated tria The descent of the inferior border (D third arro.) associated w th down ward notch in the upper precordial traces (E and F second arrow) is probabl due to descent of the mitral leaflets or of the aortic annulus (see text) The sharp down trokes in the uprasternal and upper axillary records (E and F third arrow) are probably due to runoff of blood from the aorta and from the left subclavian artery

It may be noted that the three precordial deflections which have thus far been dis cussed are almost simultaneous All of these motions (left ventricular recoil re duction in cardiac volume and expansion of great vessels) are related to a single phenomenon the onset of left ventricular ejection

b *Motions during the rapid phase of the carotid upstroke* The abrupt rise in the carotid pulse began 0 11 to 0 145 second after the beginning of the QRS the average value was 0 126 Rapid ejection as judged from the carotid pulse ended 0 1 to 0 25 second after the start of excitation the average value was 0 205 Both the onset and cessation of the rapid upstroke oc curred approximately 0 01 second earlier in the older than in the younger subjects During this period two precordial deflec tions regularly occurred (Table IV)

1 *The large left precordial and epigastric downstrokes* These movements occurred earlier and were larger in the lower than in the upper precordial regions both in absolute deflection and in relation to the total size of the tracing (Table II Figs 3 D 4 B and C and 5 A) They were somewhat greater in the lower left para sternal than in the mid-clavicular line and were very variable both in regard to size and time of onset in the axillary line In the epigastric traces this deflection was prominent the amplitude was about three fourths of the total size of the trace (Figs 4 D and 5 B)

Skinner[4] has shown that this deflection is diminished in patients with left ventricular failure and usually increases as improvement occurs.

Comment. This large inward motion which has the greatest magnitude of any whole movement during the cycle in some precordial areas would appear to be clearly related to the volume change of ejection. Its smaller size and later onset in the upper as compared to the lower left precordial intercostal spaces is presumably dependent on the mixture of arterial and ventricular patterns in the upper precordium.

2. *The small right parasternal upstroke.* Shortly before the end of rapid ejection as judged by the carotid upstroke outward movement was constantly observed in the right parasternal area (Table IV). In 24 of 49 records from this region a biphasic character of this motion was clearly seen (Fig. 3 A and 4 A). The first part of this biphasic outward excursion began at 0.14 to 0.19 (average 0.163) second after the beginning of excitation in the K area and at 0.16 to 0.22 (average 0.193) in the K_{15} region; the tracings in the other areas were intermediate. The amplitude of this initial portion of the K outward motion was usually small but the average size was greatest at the K_1 region and least at the K_{15} area; the intermediate tracings again displayed intermediate values. Since the total amplitude of the tracing during the cardiac cycle was greater in the lower than in the upper regions, the relative size was considerably larger in the K_1 and K records than in the tracings from the lower right parasternal intercostal spaces.

The second portion of this biphasic upstroke was much larger than the first. It will be considered later.

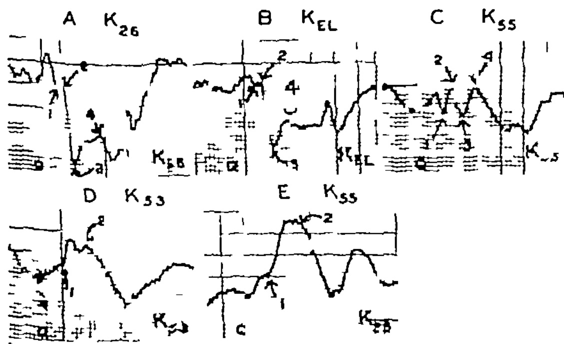


Fig. 3. H. P., normal 26-year-old man. Time lines 0.02 second. The record begins and ends at the onset of the P. Q indicates the start of the QRS of the ECG. The recoil movement as left ventricular ejection starts are small in the left parasternal and epigastric areas (A and B, first arrow) but larger in the lower left anterior axillary region (C, first arrow). The almost simultaneous motions of arterial expansion are readily seen in the high axillary and suprasternal record (D and E, first arrow). The inward motion of ejection is marked in the lower precordial traces (A, B, C, second arrow) but not in the supracardiac areas (D and E). The prominent upstroke in the infracardiac regions (third arrow, A, B, C) associated with a downstroke in the upper axillary trace (second arrow, D) is ascribed to change in shape as the mitral leaflets are pulled toward the apex. Late systole backward and/or headward motion (fourth arrow, A, B, C) and arterial runoff (second arrow, E) are seen.

Comment. The observation that this small right parasternal outward deflection which occurs during the latter part of rapid ejection is consistently earlier and greater over the upper than the lower intercostal spaces in normal persons would suggest that it may be related to some event which transpires in the right atrium. All of the dogs displayed one or more upstrokes in the pressure velocity traces of the two atria at approximately this time of the cycle. The abruptness of these motions make it improbable that atrial filling is responsible. The other possible cause of this precordial motion would appear to be bulging of the tricuspid valve into the right atrium as the pressure in the ventricle approaches its peak.

c. *Motions during reduced ejection.* The rapid phase of the carotid upstroke ends at approximately 0.21 ± 0.03 *second after* the beginning of excitation. During the next few hundredths of a second several different movements were noted (Table IV).

1, 2. *General outward motion.* At 0.215 ± 0.035 second after Q or 0.09 ± 0.02 second after the onset of the carotid upstroke, two different movements appeared to occur (Table IV). One of these was a *large outward motion in the K_1 area.* In most subjects the onset of this deflection could be defined (Figs. 3*G* and 4*A*) but occasionally it was fused with the preceding upstroke which began about 0.04 second earlier. In the left precordial region the preceding movement which started earlier than 0.20 second after Q was normally absent but most of the tracings displayed either a small outward motion (Fig. 4, *B* and *C*) or a sudden decrease in the slope of the inward movement of ejection at the time the second and larger component of this outward motion appeared in the right parasternal area. In the latter region this movement was greater in the upper than in the lower intercostal spaces even though the total amplitude of the trace was larger in the latter area. Tucker, Knowles and Eddleman[7] has shown that a movement occurring at the same time as this one is markedly exaggerated in the *left precordial area* in most patients with mitral insufficiency.

The other motion observed at this time was an *outward deflection in the epigastric region* (that is, forward or downward motion of the inferior border of the heart). This occurred in 18 of 20 records and was *larger on the average than in any of the* left precordial areas but was much smaller than the large motion in the right parasternal region (Figs. 4*D* and 5*B*). The supracardiac tracings sometimes displayed a small downstroke at this time (Fig. 5, *D* and *E*).

The atrial pressure velocity tracings of *the dogs displayed two movements* (Table I, Fig. 2) which appeared to correspond to those seen in the human subjects. Aside from the previously mentioned quick upstrokes ascribed to bulge of the atrioventricular cusps, one or more abrupt downstrokes and a later gradual upstroke were observed.

Comment. It would seem that two different mechanisms are responsible for the outward motion which occurs during the early phase of reduced ejection. The descent of the inferior border of the heart (upstroke in epigastric traces) at a time when the ventricles are expelling blood indicates that *the reduction in volume is being masked by a change in the shape of the ventricular cavities.* The decline in the atrial pressure velocity traces of the dogs suggests that the *atrial floors* (atrioventricular valves) are being pulled toward the ventricles. Additional shortening of the papillary muscles and/or of the superficial fibers which pass from the rings of these valves to the apex would account for the phenomena observed in both species.

The other motion seen at this time was largest *to the right of the sternum in the* upper intercostal spaces. This suggests that it is related in some way to events which occur in the right atrium. Since Brecher[4] has shown that this chamber fills rapidly during ventricular systole, it seems probable that such filling is responsible for this relatively large outward motion at a *time when ejection is still occurring.* This conclusion is supported by the finding of a slow upstroke in both atrial velocity traces of the dogs. Because the atria are situated behind the ventricles, atrial filling could likewise account for the small forward motion observed at this time in most of the left precordial traces. The quantita-

tive balance between the respective rates of ventricular emptying and of atrial inflow would determine whether there is an actual outward movement or a decreased inward deflection in the left precordial areas

The increased prominence of this motion in patients with mitral insufficiency offers further evidence that atrial filling is concerned

Consideration of the abnormal precordial motions which are commonly seen in patients with cardiac disease is beyond the scope of this communication However it may be mentioned that there is evidence which will be presented in future reports indicating additional causes of paradoxical (i e outward) motion during late ejection in such patients

3 *Late inward motions of the precordium* At approximately 0 25 second after the beginning of excitation and about 0 15 second before the carotid incisural notch inward excursion of one or more of the K areas was seen in most subjects (Table IV Figs 3 H and 5 A) This was sometimes followed by a small outward motion in the same regions Downward deflections were likewise encountered in 17 of 20 epigastric traces (Fig 5 B) and in more than half of the records from the K₄ K and K areas

It is uncertain whether an analogous movement was observed in the dogs As has been mentioned all of them displayed an upstroke in the previously declining ventricular velocity traces However this change appeared in the animals at a relatively earlier time than the late inward systolic motion of the precordium in the human subjects

Comment These motions are probably mainly of left ventricular origin because they are often exaggerated in persons with left ventricular hypertrophy It would appear that they are related to terminal contraction of the left ventricle or of both ventricles pulling the whole heart or possibly the interventricular septum backward and thus causing the inward motion at the K points Similarly a headward pull by both ventricles on the inferior border of the heart would account for the downstroke in the epigastric records

However since ejection is still proceeding—although at a slow rate—at this time the distinction between the change in volume of ejection and the postulated terminal changes in shape due to ventricular activity cannot be made with certainty

4 *Inward motion in the suprasternal notch* All of the normal subjects exhibited a large late systolic downstroke in the suprasternal tracing and 9 of 10 in the record from the second intercostal space in the anterior axillary line (K₁) (Table IV Figs 3 I 4 E and 5 E) Such tracings from the second and third left precordial intercostal spaces which had a general arterial pattern also displayed a large downstroke at this time (Fig 4 F)

During late systole the ventricular velocity traces of the dogs exhibited a slow decline which was sometimes interrupted by a slight upstroke or by a lessening of the slope of the downstroke

Comment This particular motion occurred in records which had the configuration of an arterial pulse wave When present it was of large amplitude and corresponded to the late systolic downstroke in the pulse wave record Therefore it is to be assumed that this movement was related to runoff from the aorta and in the case of K₁₂ trace perhaps from the subclavian artery also The possibility that a terminal downward pull on the semilunar rings also contributed to this deflection cannot be excluded The tendency toward an upstroke in the ventricular traces of some of the dogs suggests that this may have been an additional although minor factor

IV SEQUENCE OF MAJOR INWARD PRECORDIAL MOTIONS Although slight individual differences were noted a relatively constant general pattern of inward movement was observed (Table II) The upper and then the lower right precordial regions displayed the first main downstrokes Successive large inward motions were then seen in the lower left parasternal and epigastric areas the upper left parasternal and apical regions the upper left midclavicular the lower left axillary and the upper left axillary areas The time of inward motion in the left axillary region varied widely in the different subjects but in all of them the major downstroke of ejection occurred last in this area

Comment These observations indicate that changes in shape are occurring

ventricles even while their volumes are diminishing rapidly It would seem that while certain fibers are undergoing rapid shortening others are either shortening more slowly or are actually being stretched The general sequence appears to be (1) descent of the tricuspid ring (2) displacement of blood leftward (possibly due to septal shortening) (3) ascent of the apical and inferior margins with headward displacement of blood and finally (4) inward motion of the lower and then the upper portions of the left border The relatively sustained outward motion of the left axillary region during the early part of rapid ejection points toward rounding of the left border due to leftward movement of the septum ascent of the inferior border and possibly downward motion of the mitral ring

Discussion

The motions observed in the two species appeared to correspond well in most respects but not in all In the human subjects the three precordial movements (recoil decrease in volume and arterial expansion) as left ventricular ejection began were reflected in the respective abrupt rise and fall in the velocity tracings from the aorta and from the left ventricle of the dogs The descent and bulge of the closed tricuspid valve of the dogs appeared to have analogues in the right parasternal area of the human subjects An indirect indication of descent of the mitral cusps in the form of paradoxical (outward) motion of the inferior border was seen in the human subjects and direct evidence of such a motion was found in the animals In both species evidence of atrial filling was noted during the latter part of ventricular ejection

No conclusive sign of bulge of the mitral valves was seen in the human subjects despite the clear evidence for the presence of this phenomenon in the dogs The motion possibly due to elastic recoil of the aorta in the dogs was not regularly observed in the *suprasternal or upper precordial* areas of man

The data appear to offer some elucidation of the contour of the pressure pulse *in the ventricles* and large arteries After the shoulder which terminates rapid ejection there is a further rise to the highest absolute pressure which is reached during reduced ejection This late increase in pressure seems to be dependent on cardiac rather than peripheral factors because the corresponding rise in the velocity curve in the ventricles usually precedes that in the aorta and pulmonary artery (Table I) It does not seem probable that additional fibers are entering into contraction or that there is a sudden increase in the strength of contraction at a time so long after the end of excitation A more likely explanation of the *rise in pressure during reduced ejection* is given below

According to the Laplace equation

$$\text{pressure} = \frac{\text{tension}}{\text{radius}}$$

Thus if the tension or strength of contraction remains constant the pressure will rise as the volume and hence the radius decreases The quantitative significance of this equation will obviously be modified by such factors as the irregular shape of the ventricular cavities the peripheral resistance the rate of runoff of blood and the rebound of the great vessels However the principle is applicable and this explanation is in keeping with the observation that the change in velocity in the ventricles usually preceded that in the great vessels and is therefore presumably of cardiac origin

During ejection as in isometric contraction successive areas of musculature appear to reach their contractile peak at different times The changes in shape so induced may mean that despite the reduction in ventricular volume certain fibers are now stretched more than at an earlier phase of ejection The extent to which the occurrence of such additional stretch in fibers which had previously begun to shorten may cause them to contract with greater vigor is uncertain There is evidence that such a phenomenon may occur in cardiac muscle[9] If this effect which might be called *the secondary length* does like the initial length play a role *in the force* of the subsequent terminal contraction it may perhaps also contribute to the rise in pressure which occurs during reduced ejection and thus to the contour of the ventricular and arterial pressure pulses The relation of such phenomena to

the terminal systolic precordial movements is obscure

These concepts of cardiac motion are in many respects similar to those of Rushmer[18] and his colleagues who utilized entirely different methods. The observation that the phenomena observed in two separate species studied under varying experimental conditions and with completely different techniques are susceptible to the same interpretations increases the likelihood of the validity of the general concepts. On the other hand this evidence in regard to the genesis of the precordial motions is of indirect nature and studies by more direct methods are desirable. Attempts along these lines are currently in progress.

Summary

The precordial *movements (kinetocardiograms)* of normal adults during ventricular ejection have been analyzed in relation to the velocity of pressure change in the cardiac *chambers and great vessels of dogs.* The data point toward the following general sequence of cardiac motion.

A. *During the period between the onset of left ventricular ejection and the start of the carotid upstroke.* Three almost simultaneous precordial movements occur at this time. (1) Left ventricular recoil occurs and produces the normal brief apex tap as the left side of the precordium moves out. (2) As both ventricles eject, there is a large inward motion of the right parasternal region. This is apparently produced by rapid descent of the closed tricuspid valve. (3) The expansion of the aorta produces an outward motion in the suprasternal notch and sometimes *in the upper intercostal* spaces. The analogous movements in the dog are the respective rise and fall in the aortic and ventricular pressure velocity curves and a *sharp dip* in the right atrial velocity record.

B. *During the rapid phase of the carotid upstroke.* (1) The volume change of ejection causes large inward motion of the left precordial and epigastric areas. (2) Outward movement of the upper right parasternal region occurs. This is apparently due to bulge of the tricuspid valve which is shown in dogs by an ascent of the atrial pressure velocity tracing. (3) In dogs the aortic velocity record, having passed its peak, shows a small upstroke which is possibly an artifact but which may be due to elastic rebound. A similar motion has not been seen regularly in tracings from human subjects.

C. *During reduced ejection.* (1) A large upstroke in the region over the right atrium and a much smaller outward movement (or diminished inward deflection) in the left precordial area is ascribed to atrial filling. (2) An outward motion of the epigastrium and sometimes of the lower precordium occurs. This is probably related to descent of the mitral annulus since the left atrial velocity record of the dogs shows a downstroke at an approximately corresponding time. (3) The terminal precordial systolic movements are somewhat variable but usually include inward *motion (further decrease in ventricular volume)* of the left precordial and epigastric areas. (4) Since blood leaves the aorta more rapidly than it enters, the *tracing from the suprasternal notch moves* inward.

The pressure velocity tracings from the ventricles and from the great arteries of *the dogs show an upstroke as the phase of* reduced ejection begins. This is ascribed to the rise in pressure which results from a decrease in volume when fiber tension *is relatively constant (Laplace effect).*

During ejection certain changes in shape occur and appear to cause stretch of some of the fibers. The extent to which such *secondary length may influence the terminal* contraction of these fibers is uncertain.

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Case reports

Aortic atresia
A case report and a review

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The pathologic features of congenital aortic atresia have been well documented but most previous reports have been characterized by a paucity of associated clinical data.

In this case a full clinical evaluation which included physical examination, electrocardiogram, vectorcardiogram, phonocardiogram, thoracic roentgenograms, retrograde aortogram, and cardiac catheterization was possible prior to death and could be correlated with the pathologic specimen.

Case report

L. J., an 11-day-old Negro female infant, was admitted to the University of Florida Teaching Hospital on Oct. 22, 1960, because of dyspnea which had been present for 1 day. The mother had had a normal gestation and labor. The home delivery, assisted by a midwife, was uncomplicated. Breathing and crying were spontaneous. A cleft lip and palate were noted at birth. Twenty-four hours prior to admission the infant developed tachypnea, dyspnea, lethargy, and anorexia. Grunting respirations developed a few hours before admission.

The family history was noncontributory.

Physical findings. At the time of admission the vital signs were: flush blood pressure—right arm 118, left arm 114, right leg 116 mm. Hg; pulse 130 per minute, strong and regular; respirations 84 per minute; temperature 36 C. rectally. The weight (3.2 kilograms), length (51.5 cm.), and circumference of the head (35.5 cm.) were all normal for the age of the patient. The general appearance was that of an acyanotic, restless infant with severe dyspnea and tachypnea. A unilateral cleft of the left lip extended to the gingiva and into the hard and soft palates.

No thrill was discernible in the suprasternal notch or over the precordium, but a strong thrusting right ventricular beat was palpated at the second and third left intercostal spaces. A Grade 3/6 holosystolic decrescendo murmur maximal at the fourth left intercostal space, but well transmitted to the apex, base, neck, axilla, and left back, and a Grade 1/6 apical mid-diastolic murmur were noted. An ejection click was heard intermittently at the fourth left intercostal space. The second sound in the pulmonic area was very loud and single. The brachial, carotid, and femoral pulses were vigorous and bounding. The lungs were clear to auscultation. The liver was palpable 4 to 5 cm. below the right costal margin.

The remainder of the physical examination gave normal findings.

Laboratory data showed a hemoglobin of 16.4 Gm. per 100 ml. and a hematocrit of 50 volumes per cent.

Roentgenologic examination (Fig. 1) showed marked cardiac enlargement with a widened superior mediastinum and prominent convex right heart border secondary to right atrial enlargement, an upward turned apex, and complete filling of the retrosternal space by right atrial and right ventricular dilatation. The pulmonary vasculature was increased and the aorta was not outlined.

There was no roentgenologic evidence to suggest left ventricular or left atrial hypertrophy.

The electrocardiogram (Fig. 2) showed sinus rhythm at a rate of 130 per minute. The P-R interval was 0.10 second, QRS duration 0.08 second, Q-T interval 0.39 second, and the mean QRS vector in the frontal plane +110 degrees. Right atrial hypertrophy was indicated by tall (0.4 mv.) peaked

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Fig 1 Anteroposterior (left) and lateral (right) thoracic roentgenograms of the 11-day-old female infant who was in congestive heart failure with congenital aortic atresia

narrow Ι es in Lead II and V together with qR pattern Lead V and V R ht entricular hypertrophy (or t he overload) w indicated by an abnormall high ratio of R t RS (80 per cent) and the qR pattern in Lead V nd V depressed S-T segment in Lead V nd V and positi T w es in the right precordial lead

The ectorcardiogram (Fig 2) howed the direct n of inscription of the QRS-E loop to be clock w se the horizontal nd frontal planes The initial forces of the QRS ector were d placed posteriorly superiorl and lightly to the left The body of the QRS loop w d placed a teriorly inferiorly and neither left nor right The QRS loop inscribed ery narrow arc the horizontal nd frontal planes nd wide arc in the sagittal plane

The QRS-T angle was narrow which indicated a concordant (normal) relation hip of the mea QRS-E and T E ectors

The Ι E loop wa indi tingui hable in all planes

The phonocardiogram (Fig 3) howed a moderate decrescendo holosystolic murmur accompanied by a prominent dela ed systolic ejection sound (QE time 0 12 second) which was maximal in the fourth left intercostal pace The first sound was accent uated The murmur recorded well over the entire precordium The second sound was ingle and accent uated Third and fourth sounds were present t the apex.

A retrograde aortogram (Fig 4) was diagnostic of aortic atresia. At the time of aortography the oxygen saturation of the blood which was taken from the right brachial artery with the patient breathing 100 per cent oxygen was 92 per cent (spectrophotometer Hickam and Fra ser method)

H pi al cou se l pon admis ion the patient wa treated immediately with digitalis diuretics and oxygen and be re-pr nded within 24 hours On the third day of hospitalization retrograde aortograph was performed and the ant tolerated the proce On the eighth day in the hospital the respir tory rat increased from 65 to 105 per minut nd the ndit on of the patient began to deteriorate She tarted t ha generalized seizures spells of apnea and bouts of brad cardia Cardiac catheteri zatic was performed on the tenth day in the hospital The patient condition worsened and he died during the latter part of the catheteriza t n

Postmortem examination of cardiovascular system The pericardial cavit contained about 15 of yellow h clear fluid The heart which weighed 27 gram L in trans erse position th the apex at the anterior axillary line The right entricle wa extremel prominent and the right trium was dilated pproximately tw to three times the normal ze (Figs 5 and 6)

The al e of the forame ovale was competent but because it was not adherent along the terior margin it allowed a 3-mm opening (Fig 6) The right entricle was hypertrophic and mea ured 7 mm in thickness under the tricu pid val The septal cu p of the tricu pi l v lve was cleft It had gnarled redun lant ti ue and was pla tered to the inferior margin of 1-cm crescent-shaped ostium primum type of a rial septal defect (Fig 6) The tricu pid al ppeared to be incompetent beca se of the cleft septal cu p and the dilated orifice of the tricu pid valve which mea ured 4 7 cm in circumference The other components of the tri cu pid al e and the entire pulmonic al e were normal At the bifurcation of the pulmonary artery was a large patent ductus arteriosus which meas ured 5 mm in idth and 2 mm in length The pulmonary ein ere connected t left trium which wa normal in ze There was a left trial-right entricular communication through the cleft septal leaflet of the tricu pid alv and cleft in the hypopla tic mitral alv (diameter of 4 mm) which lay above the minuscule, 2 mm-deep left entricle. The ascending aorta had normal rela tion hip t the pulmonary artery but was hypo-

plate (Fig. 3) it measured 4 mm. in diameter up to the level of the innominate artery and then was 11 cm. in diameter. In the atretic aortic valve, which measured 4 mm. in diameter, three minute completely fused cusps were discernible. The left and right coronary arteries, their ostia, and their branches traversed a normal course. The great vessels of the aortic arch were normal in diameter and position.

Postmortem examination of lungs. The lungs, which weighed a total of 73 grams, showed extensive atelectasis grossly. Microscopic sections of the lungs showed moderate congestion, extensive atelectasis, scattered petechiae, and had the overall appearance of Swiss cheese emphysema. The alveoli adjacent to the bronchioles were plural, tortuous, and kinked. The thickness of the pulmonary arteriole wall in relation to total diameter was normal for the infant's age.

The two pertinent diagnoses were (1) aortic valvular atresia and (2) ostium primum type of atrial septal defect with cleft tricuspid and mitral valves.

Discussion

Aortic atresia, which falls within the spectrum of hypoplasia of the left side of the heart,[1] is thought to be a rare congenital cardiac anomaly. The number of cases reported in the literature seems to approximate 170. However, one is impressed by the divergence of the recorded tabulations; this is caused in part by the fact that in the eighteen eighties the term *atresia of the aorta* had a much broader connotation and included cases of coarctation of the aorta.[3]

Lanfant[4] attributes the earliest report of a case of aortic atresia to Farre in 1814. This and succeeding reports[1, 4-11] were essentially pathologic descriptions. Only in the last few years have clinical studies[7, 12] been reported in patients with this anomaly.

Theories of the embryogenesis of aortic atresia have been summarized by Sanchez Cascos and Chavez.[7] There appears to be no correlation with birth weight or any particular prenatal factor. Brekke[3] has reported 2 cases in one family.

Although our patient was a female, several authors[5] have shown that the sex distribution in aortic atresia is approximately 2 males to 1 female.

The early onset of cardiac failure in this infant is characteristic of aortic atresia. Keith and co-workers[2] found this defect to be the most common cause of heart failure in the first week of life.

The cleft lip and palate in our case are not unexpected since additional noncardiac anomalies have been noted to occur frequently in patients with obstructive lesions of the left side of the heart.

Although atresia of the aorta is usually thought of as a distinct entity, it is not

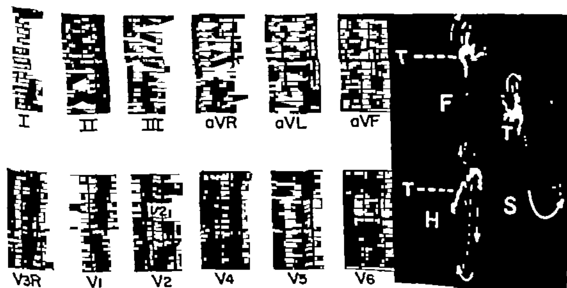


Fig. 2. *Left.* Electrocardiogram of the 11 day old female infant with congenital aortic atresia (see text for complete description). *Right.* Vectorcardiogram (Grishman cube method) taken when the subject was 15 days old. *H, S, F,* Horizontal, sagittal, and frontal planes, respectively. *T,* T vector loop. Arrows indicate direction of inscription of QRS loop (see text for complete description).

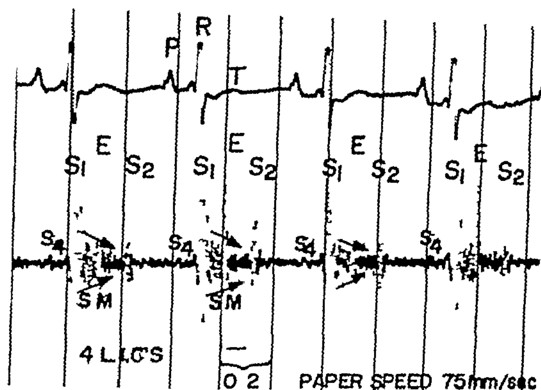


Fig. 3. Electrocardiographic Lead I (*above*) and simultaneous phonocardiogram (*below*) taken at the fourth left intercostal space in the 15-day-old female infant with congenital aortic atresia. The first sound (S_1) is accentuated. The phonocardiogram shows a moderate holosystolic decrescendo murmur (*SM*) accompanied by a delayed systolic ejection sound (*E*). The second sound (S_2) is single and accentuated. A fourth sound (S_4) was present.

surprising that our patient appeared to be acyanotic. Two separate samples of peripheral arterial blood in our case with the patient receiving oxygen by mask were 92 and 87 per cent saturated. Keith and co-workers[13] measured arterial oxygen saturations in 6 cases and 3 of these had values over 90 per cent when supplemental oxygen was administered. Thus, although cyanosis eventually develops, often in conjunction with cardiac failure, it may not be present or clinically apparent in the first few days of life.

The pulses in our patient were vigorous and bounding with the flush blood pressures over 100 mm. Hg. These are unusual physical findings since Keith and co-workers[13] and Taussig[12] both emphasize the weak or absent peripheral pulses in patients with aortic atresia.

The murmurs described in the reported cases have been variable in location and intensity, and no typical auscultatory findings have been established. Among the 38 infants with aortic atresia reported by Keith, 15 had a systolic heart murmur; the others had none. Ten of the 15 patients in the series of Noonan and Nadas[3] had nonspecific soft systolic murmurs audible over the precordium. In 3 of these 10 patients an additional mid-diastolic rumble over the apex was noted.

Our auscultatory and phonocardiographic findings (Fig. 3) correlate well. The holosystolic decrescendo murmur may be explained on the basis of tricuspid insufficiency or increased flow through the pulmonary valve or both.

The documentation by auscultation and the recording on the phonocardiogram (Fig. 3) of a systolic ejection click adds aortic atresia to the list of entities in which this may be noted. Presumably, this systolic ejection sound was caused by rapid expansion of the pulmonary artery. This expansion of the tremendously pulsatile pulmonary artery was documented by cinefluorography and supports the view that the ejection sound was of pulmonic origin. The respiratory rate was too rapid for us to observe whether the intensity of the ejection click decreased with in-

spiration and increased with expiration as is usual when the ejection clicks are of pulmonic origin The delayed onset indicates a prolonged right ventricular isometric contraction time The maximum intensity of the ejection click was at the fourth left intercostal space but it is not unusual for sounds of pulmonic origin to radiate down the left sternal border

The mid-diastolic murmur at the apex of the heart was presumably due to rapid ventricular filling during diastole since the right ventricle received the blood from both atria

Roentgenologic findings though they at times may be suggestive are not diagnostic of atresia of the aorta The marked cardiomegaly (caused by right atrial and right ventricular hypertrophy) and the increased pulmonary vascularity have been reported many times

The electrocardiogram in this case showed right axis deviation This was one of the earliest and most frequently described electrocardiographic features although Soloff[9] has reported a case in which there was left axis deviation Right atrial enlargement right ventricular hypertrophy upright T waves in the right precordial lead with flat to partially inverted T waves in the left precordial leads were prominent features (Fig 2) and were also noted by Keith and co workers There was no evidence of left ventricular activity over the precordium Slight slurring of the ascending limb of the R wave seen in Leads V_4 and V_6 (Fig 2) can also be noted in Leads V and V_6 in Keith's tracing The qR pattern in the right precordial leads is an important sign and is consistent with an enlarged right atrium and right ventricle Although the necropsy specimen showed an ostium primum type of atrial septal defect with clefting of both atrioventricular valves our tracing was not typical of the usual ostium primum defect

Our tracing showed neither first-degree heart block nor widening of the QRS interval Ley and Killian accounted for the first-degree heart block in 2 cases of aortic atresia by noting increased connective

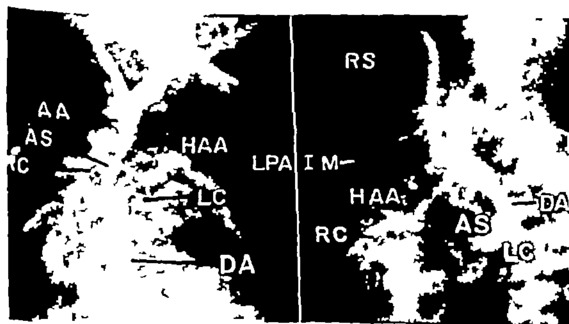


Fig 4 The retrograde aortogram taken in the 14-day old female infant with aortic atresia *Left* Anteroposterior position *Right* Lateral position The rad opaque media seen in the right subclavian artery (*RS*) internal mammary artery (*IM*) and the aortic arch (*AA*) The media is also seen in the hypoplastic ascending arch (*HAA*) small aortic sinus (*AS*) and the larger right coronary artery (*RC*) and smaller left coronary artery (*LC*) Another portion of the dye is seen in the descending aorta (*DA*) and the pulmonary arteries (*LPA* left pulmonary artery) The media also filled huge patent ductus arteriosus which is not visualized well in two frames

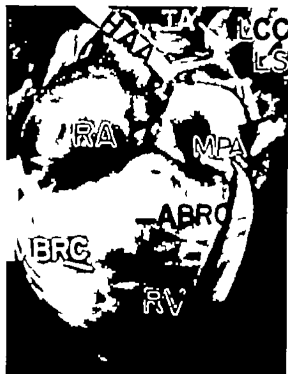


Fig. 5. An anterior view of the specimen at necropsy showing the very prominent right atrium (*RA*) and ventricle (*RV*). The hypoplastic ascending aorta (*HAA*) has a normal relationship to the grossly enlarged main pulmonary artery (*MPA*). The great vessels arising from the aortic arch, the innominate artery (*IA*), left common carotid (*LCC*), and left subclavian (*LS*) are normal in size and position. (*ABRC*, Anterior branch right coronary artery; *MBRC*, Marginal branch right coronary artery.)

tissue in the region of the bundle of His. In these same cases there was a prolonged QRS duration, presumably the result of focal degeneration and increased connective tissue in the bundle branches. One of the cases of Friedman and associates[23] revealed left bundle branch block.

In the vectorcardiogram (Fig. 2) the anterior displacement of the T wave in the horizontal plane reveals the basis for the positive T waves in the right precordial leads and flat to negative T waves in the left precordial leads. The initial QRS forces directed posteriorly in the horizontal plane cause the abnormal Q waves in precordial Leads V₆ and V. The clockwise inscription of the QRS loop in the frontal and horizontal planes is normal for the infant's age. The counterclockwise inscription of the QRS loop in the sagittal plane is usually abnormal, although at times this direction may be observed in normal newborn infants.[24] Anterior displacement of the QRS-E loop in the horizontal plane is not abnormal at this age, but the narrowness of the arc and the extreme anterior position are unusual. These findings are consistent with right ventricular hypertrophy.

The aortogram (Fig. 4) demonstrated retrograde filling of the hypoplastic ascending aorta and the large patent ductus so characteristic of this anomaly. The coronary arteries were normally situated, although transposition of these vessels has been reported in cases of aortic atresia.[7]

Retrograde aortography is probably the best and simplest way to establish the diagnosis of aortic atresia. Conceivably, the hypoplastic ascending aorta might not fill with radiopaque media, yet demonstrate the patent ductus arteriosus. In a clinically acyanotic child in congestive failure this set of circumstances might precipitate operation for transection of the patent ductus, particularly when, as in this case, bounding pulses were present.

Forward venous angiocardiography could also be diagnostic, for only in cases of atresia of the aorta would a reverse patent ductus arteriosus fill the ascending aorta.

Physiologic data obtained by catheterization of the right side of the heart (Table

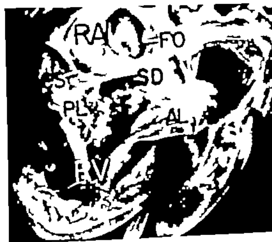


Fig. 6. View of right side of heart showing large dilated right atrium (*RA*) and large hypertrophied right ventricle (*RV*). The atrial septal defect (*SD*) is bounded below by the gnarled malformed septal leaflet (*SL*) of the tricuspid valve. *FO*, Patent foramen ovale; *CS*, Coronary sinus; *PL*, Posterior leaflet of the tricuspid valve; *AL*, Anterior leaflet of the tricuspid valve.

could be correlated with a majority of clinical and pathologic findings

Oxygen saturation in the superior vena cava was very low. This profound degree of desaturation of the systemic venous return probably is a reflection of systemic ... The large step-up in oxygen content at the right atrial level was produced by ... return of left atrial blood into the right atrium through the patent foramen ovale or through the septal defect (Fig. 6).

The inferior vena cava and right atrial oxygen saturations were similar, presumably because a stream of blood from the left atrium passed through the septal defect and incompetent tricuspid valve into the mouth of the inferior vena cava. Reflux of blood from the right atrium into the inferior vena cava during contraction of the right atrium may also have been a factor. The pressure in the right atrium was elevated with a prominent v wave which is compatible with cardiac failure and incompetence of the tricuspid valve.

In this case the right ventricle was the only ventricle which functioned physiologically. The systolic pressure in this chamber when measured varied from 35 to 50 mm. Hg. This low pressure is probably a manifestation of the poor status of the patient. The end-diastolic pressure of the right ventricle was elevated, which is consistent with cardiac failure. The right ventricle was the site of maximal arterialization, probably because most of the blood from the left atrium emptied directly into the right ventricle through the septal defect.

Our failure to enter the pulmonary artery made it impossible to evaluate the status of the pulmonary vascular bed. The oxygen saturation of blood which was taken from the left pulmonary vein was less than that taken from the left atrium, right ventricle, and right brachial artery. This paradox might be explained by poor alveolar ventilation in that segment of the lung because of the atelectasis and pneumonia which were noted at necropsy, or by a change in the physiologic state of the infant between samplings.

Table I. *Catheterization data*

Catheter position	*Oxygen content*		*Pressures (mm. Hg)*	*Time (sec.)*
	Volumes (per cent)	*Saturation (per cent)*		
Superior vena cava	1 97	18 0		0 09[illegible]
Right atrium (mid lateral)	6 38	59 0	Inspiration 14/4 a = 10 v = 14 Expiration 3 /22 v = 32	0 0935
Inferior vena cava	6 58	61 0		0 0957
Right ventricle (1)	9 31	86 0	35/2 to 12	0 1030
Right ventricle (2)			50/10 to 16	0 1041
Pulmonary vein (1) (left lower)	9 97	74 0	40/7 to 12	0 0944
Left atrium	8 56	9 0		0 1001
Brachial artery	10 79	88 0	80/30 Mean 50	0 1142
PV ——→ RA			40/20 ——→ Mean 12	0 0950
PV ——→ LA			40/18 ——→ 38/18	0 1000
SVC ——→ RA ——→ IVC			Expiration 22/16 } → Mean 12 → Mean 8 Inspiration 14/6 }	0 0953

Oxygen capacity (1) 10 83 and ( ) 12 30 volumes per cent (applies to brachial arterial sample only)
Arterial saturation 87 7 per cent
Systemic flow 0 56 L./min. } Calculated on basis of estimated oxygen consumption of 160 c.c./min./M
Index 2 4 L./min.
Resistance 7 140 dynes sec. cm.$^{-5}$

PV Pulmonary vein; RA, Right atrium; LA, Left atrium; SVC, Superior vena cava; IVC, Inferior vena cava. Arrows signify ... of catheter.

The pulmonary venous pressure was elevated with a distinct pressure gradient between the left pulmonary vein and the right atrium

The systolic pressures in the right brachial artery were higher than the previously recorded pressure in the right ventricle Again these differences must be explained by the changing physiologic state of the infant The wide variation in pulse pressure (50 mm Hg) was probably caused by a rapid fall in aortic pressure with ventricular diastole since conceivably the blood in the aorta might re enter the pulmonary vascular bed

In aortic atresia the hypoplastic mitral valve and the minute left ventricle have no functional significance Many cases of aortic atresia have concomitant mitral atresia

The systemic cardiac index was slightly below normal values and again reflects the terminal cardiac failure Consequently the calculated systemic resistance was very high

It has been noted by others [8] that those infants with the smallest atrial septal defects are the most cyanotic and have the shortest lifespan presumably because the pulmonary venous return to the right side of the heart is severely compromised This observation led some to suggest the creation of an atrial septal defect to improve the left to right shunt which is essential for survival As pulmonary flow increases systemic arterial saturation increases and concomitantly peripheral venous saturation would tend to decrease

The vast majority of patients with aortic atresia die during the first week of life The clinical course of our patient was unusual in that the infant lived 21 days Only an occasional patient has lived longer DuShane[15] reported a patient who lived 110 days, and Shub and Speer [4] one who survived 5 months

Summary

A case of congenital aortic atresia is presented in which the physical examination electrocardiogram thoracic roentgenogram phonocardiogram vectorcardiogram retrograde aortogram and cardiac catheterization were obtained prior to death of the patient at 21 days

The clinical findings are correlated with the pathologic specimen and compared with the data previously reported in the literature An unusual anatomic feature was the coexistence of a persistent common atrioventricular canal malformation

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Hemodynamic observations in a case of carcinoid heart disease associated with an atrial right-to-left shunt

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The cardiac abnormalities usually associated with the carcinoid syndrome have been well defined as consisting of an endocardial fibrosis on the right side and associated lesions of the pulmonic and tricuspid valves.[1] Cutaneous vasodilatation in these patients commonly results in a reddish violet discoloration of the skin[2] which usually can be distinguished with ease from the cyanosis due to arterial oxygen unsaturation. It is not generally appreciated that these types of skin discoloration may coexist, as in the patient now reported upon who had carcinoid heart disease with a right-to-left shunt at the atrial level. This combination is a most unusual occurrence and, to our knowledge, hemodynamic observations on such a case have not been recorded previously.

Case report

A 50-year-old white married woman had enjoyed good health until 1957, when she developed frequent reddish blue facial flushes and eventually permanent facial discoloration. In 1958 her bowel movements became more frequent, averaging two to five normal-appearing stools daily. Later that year she began to have easy fatigability, dyspnea, palpitations, and light to moderate dependent edema. She took digitalis leaf 0.1 Gm. daily for 1 year without apparent symptomatic benefit. At no time did she have chest pain, cough, wheezing, or orthopnea.

She had never had evidence of acute rheumatic fever, nor were heart murmurs ever detected until 1958. The last physical examination before the onset of the present illness was in 1956, prior to a minor gynecologic procedure.

When she was admitted to the National Heart Institute on Nov. 1, 1960, the temperature was 37 C., pulse 76 per minute, blood pressure 125/85 mm. Hg, and respirations 20 per minute. There was a constant noticeable reddish violet discoloration of the face, with [illegible] similar coloring over the upper trunk and the extensor surfaces of the extremities. The fingers were slightly clubbed, with increased mobility of the nail bed. In the jugular veins there were large A [illegible] es and very prominent systolic waves. The lungs were clear to percussion and auscultation. The cardiac rhythm was regular. There was a right ventricular heave and a systolic thrill along the left sternal border which increased with inspiration. The first sound at the apex was very faint. A right ventricular diastolic gallop was present. Heart murmurs were graded in intensity on a scale of 1 to 6. There was a Grade 4 blowing holosystolic murmur over the sternum. A Grade 2 ejection type of murmur was best heard at the pulmonic area (Fig. 1). With inspiration, a faint presystolic rumbling murmur could be heard along the left sternal border in the fourth intercostal space. The liver was palpable 13 cm. below the right costal margin and was firm, nodular, and not tender. No hepatojugular reflux or pitting edema was noted.

No method was found to anticipate or precipitate flushes in this patient. During a flush the pulse rate increased slightly, but the blood pressure did not change significantly. The skin discoloration described above intensified greatly and deep cyanosis of the lips and nail beds appeared.

Laboratory observations included a hematocrit [illegible] 49.5 per cent. Normal values were obtained for routine urinalyses, blood urea nitrogen, fasting blood

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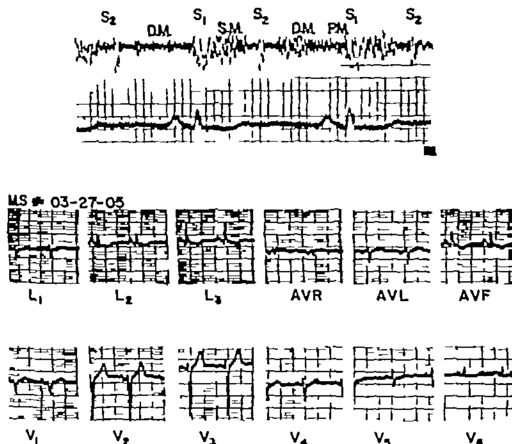
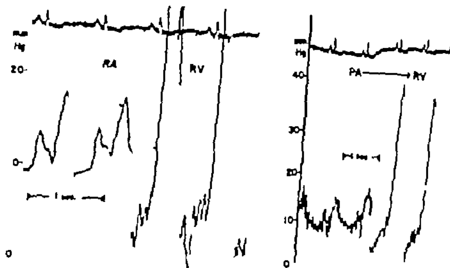


Fig 1 Phonocardiogram taken in the fourth intercostal space at the left sternal border *S* First sound. S_2 Second sound *SM* Systolic murmur *DM* Diastolic murmur *PM* Presystolic accentuation of diastolic murmur Electrocardiogram showing right axis deviation digitalis effect, and P wave abnormality compatible with right atrial enlargement

sugar white blood cell count serum electrolytes total protein albumin serology and serum glutamic oxalacetic transaminase Average urinary excretion of 5-hydroxyindoleacetic acid on multiple determinations was 396 mg per 24 hours (normal 2 to 9 mg) Liver damage was evidenced by serum bilirubin of 1 0 mg per 100 ml of which 0 9 mg was indirect an alkaline phosphatase of 20 King Armstrong units and Bromsulphalein retention of 16 per cent in 45 minutes An [illegible] ray film of the chest showed slight non specific enlargement of all cardiac chambers Multiple small filling defects [illegible] the small intestine [illegible] visualized on gastrointestinal roentgenograms An electrocardiogram was interpreted as showing right axis deviation digitalis effect and an abnormality of the P wave compatible with right atrial enlargement (Fig 1)

Catheterization With the patient lightly sedated cardiac catheterization was performed through the right saphenous [illegible] The catheter was passed initially into [illegible] peripheral pulmonary artery where the mean wedged pressure was 4 mm Hg The pressure in the main pulmonary artery was 15/8 mm. Hg (mean 11) and when t[illegible]ter was withdrawn into the [illegible]ght ventricle [illegible] gradient of 25 mm Hg was recorded across the pulmonic valve (Fig 2) A second catheter with [illegible] platinum electrode tip but also suitable for recording pressures was then introduced into the right atrium where the pressure contour was typical of that recorded in cases of tricuspid insufficiency The mean right atrial pressure was 12 mm Hg the A wave was 13 mm. Hg and the V wave was 18 mm Hg Sequential recordings of right atrial and right ventricular pressures revealed a mean diastolic gradient of 9 mm Hg across the tricuspid valve (Fig 2) The presence of tricuspid insufficiency was confirmed by the early detection of an indicator substance ascorbic acid by the atrial electrode catheter when the indicator was injected into the ventricle. A krypton[85] inhalation test demonstrated that no left-to-right circulatory shunt was present A platinum wire electrode was then placed into the left brachial artery through a Cournand needle and an indicator-dilution curve was recorded after the injection of ascorbic acid into the inferior vena cava (Fig 3) The early primary curve was formed by the indicator which crossed an intracardiac defect thereby bypassing the lung and the secondary curve is the result of the indicat



F . Left Sequential tracing of right atrial (RA) and right ventricular (RV) pressures demonstrating mean diastolic gradient across the tricuspid valve of 9 mm Hg Right Pull-out tracing from the pulmonary artery (PA) to the right ventricle (RV) demonstrating systolic gradient of 25 mm Hg across the pulmonic valve

traversed the pulmonary circulation When the indicator was injected distal to the right atrium only the secondary curve was recorded indicating that the right to-left shunt was through an interatrial defect The brachial arterial pressure was 140/85 mm Hg The systemic arterial oxygen saturation was 87 per cent at rest and rose to 90 per cent when the patient breathed 100 per cent oxygen for 10 minutes The atrial septum was probed extensively with the catheter but the interatrial defect could not be crossed

In summary the catheterization findings demonstrated peripheral arterial unsaturation and an interatrial defect with a right to-left shunt right atrial and right ventricular hypertension valvular pulmonic stenosis and tricuspid stenosis and insufficiency

Discussion

The catheterization findings of tricuspid stenosis and insufficiency and pulmonic stenosis are consistent with those in cases of carcinoid heart disease previously reported [6,7] Left heart catheterization was not performed in this patient because she was considered to be too ill to tolerate such a procedure and because of the absence of clinical evidence of valvular disease on the left side

The endocardial fibrosis seen in this syndrome is histologically specific and can be readily distinguished from endocardial fibrosis due to other causes [4] Its cause is not known The most plausible theory presented however is that the hepatic metastases liberate a substance which either directly or indirectly produces fibrosis of the endocardium It is likely that this substance is serotonin (5 hydroxytryptamine) The scarcity of left heart lesions could then be explained by the abundance of monoamine oxidase in the lungs which oxidizes most of the free circulating serotonin before it comes into contact with the endocardium on the left side Sjoerdsma and associates [8,6] were unable to detect significant differences between arterial and venous levels of serotonin presumably because most of this amine is bound to platelets and the assay of small amounts in plasma is not feasible technically It is the free plasma serotonin that is available to be oxidized in the lungs or to produce endocardial disease Efforts to produce endocardial lesions in experimental animals with serotonin were unsuccessful until

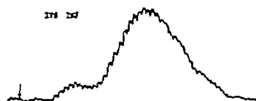


Fig 3 Indicator-dilution curve after injection of ascorbic acid into the inferior vena cava (IVC) as recorded in the left brachial artery The early appearance of ascorbic acid is compatible with right to-left shunt

Ross and co-workers[1] recently infused this amine directly into the ascending aortas of young dogs. The lesions they produced, however, did not resemble either histologically or by their distribution those lesions seen in cases of the carcinoid syndrome in human beings.

Fibrosis on the left side may occur in the carcinoid syndrome in the absence of right-to-left shunt, but such lesions are decidedly uncommon and usually quite mild.[3,4,10] The suggestion that the cardiac lesions are entirely secondary to elevations of pulmonary arterial pressure by serotonin is probably untenable since such elevations, although observed experimentally, are not usually seen in the carcinoid syndrome even during a flush.[12]

During a flush, the lips and fingernails of this patient assumed a blue color which was characteristic of the cyanosis of arterial oxygen unsaturation, while elsewhere her skin showed the usual reddish violet flush of the carcinoid syndrome. There was slight clubbing of the fingers and excessive mobility of the nail beds. These findings prompted us to consider the possibility of right-to-left shunt and to undertake the confirmatory studies outlined above. Because she was previously free of heart murmurs and of cardiac symptoms, we considered this shunt to be through a foramen ovale which had become patent when the acquired valvular lesions caused the pressure in the right atrium to exceed that in the left atrium.

Defects in the atrial septum have been described previously in conjunction with malignant carcinoids. McKusick reported a case diagnosed at autopsy with a large patent foramen ovale and fibrosis of all four heart valves. Wolfe and co-workers[14] reported a case with severe valvular lesions on the right side. At autopsy, a small patent foramen ovale and mild fibrosis of the mitral valve were discovered. Fischer and Lindeneg[1] presented data derived at necropsy in a case in which a slit-like foramen ovale was associated with fibrosis of all four heart valves and similar mild fibrosis of the coronary arteries. Spain reported upon three cases of malignant carcinoid in which a patent foramen ovale was discovered at autopsy. In none of these cases was there any evidence of valvular or endocardial disease. In the first patient reported by Sjoerdsma and associates,[1] arterial oxygen saturations of 87 to 91 per cent were recorded. The possibility of a small right-to-left shunt through a patent foramen ovale was considered but remained unproved because insufficient data were available. It is surprising that patency of the foramen ovale, which is seen as an incidental finding at as many as 20 to 25 per cent of autopsies,[4] has not been observed more frequently in the cases of malignant carcinoid in which autopsy was performed.

Adherents to the theory that circulating serotonin is the cause of the endocardial fibrosis and that the rarity of lesions on the left side is due to serotonin oxidation in the lungs refer to the occurrence of mitral and aortic fibrosis in the presence of communicating atria as a fact supporting this theory. The serotonin-bearing venous blood would thus avoid exposure to monoamine oxidase by direct passage into the left atrium. This study has documented that significant blood flow may occur through such a shunt.

Furthermore, as demonstrated here, cyanosis which appears in the carcinoid syndrome may not always be due to the flush phenomenon. It may be due to arterial oxygen unsaturation, in which case it should be recognized as such.

Summary

An unusual case is presented in which the cardiac lesion of the malignant carcinoid syndrome with pulmonic and tricuspid valvular disease was complicated by a right-to-left shunt at the atrial level, probably through a patent foramen ovale. These findings were documented by right heart catheterization. The probable explanation for the development of this situation is discussed.

We are grateful for the helpful suggestions of Dr. Albert Sjoerdsma, Dr. John A. Oates, and Dr. Eugene Braunwald.

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Clinical pathologic conference

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Clinical abstract

DR. HEATH The patient whose case is to be discussed was a 51 year-old man who was well apart from vague attacks of lumbago from time to time until September 1953 At that time he had another attack of pain low in the back which he treated with lotion Pain and stiffness developed in the joints, and he began to sweat and feel ill His general practitioner prescribed aspirin for this but after a brief abatement of symptoms the pains in the joints grew worse and a macular rash developed over his body Six weeks later his eyes began to feel gritty and became bloodshot He attended an eye hospital was admitted as an inpatient and was given atropine and cortisone eye drops There was some improvement and therapy with salicylates was continued One morning while still an inpatient he woke up with severe nausea vomiting and vertigo The salicylates were stopped and phenobarbitone was substituted He was discharged from the hospital but developed sensations of irregular beating of the heart At times he felt as though his heart were stopping On account of these new symptoms he was admitted to another hospital

Clinical examination on admission on Dec 1 1953 showed him to be a well built man with a morbilliform rash on the upper trunk and arms His throat and tongue were clear The mucous membranes showed no evidence of anemia No enlarged lymph nodes were palpable There was an intense inflammatory injection of both conjunctivae There was circumcorneal injection and small yellow nodules were present in the sclera He had swelling and stiffness of the wrists ankles and fingers especially the proximal interphalangeal joints Examination of the cardiovascular system revealed no pitting edema of the ankles or sacrum There was no distention of the veins of the neck The liver was not palpable The radial pulse rate was 108 per minute and the rhythm was regular The systemic blood pressure was 170/90 mm Hg The apex beat was palpable in the fifth left intercostal space in the mid-clavicular line The cardiac impulse was normal There was a split first sound a normal second sound and a loud clicking sound At one time it was thought likely that he had a faint pericardial friction rub at the apex The respiratory alimentary and nervous systems showed no abnormality on clinical examination A teleradiogram of the chest was normal

Investigations Hemoglobin was 76 per cent (11 3 Gm per cent) Erythrocyte sedimentation rate (Westergren) was 85 mm in the first hour The color index was 0 86 The red blood cell count was 4 400 000/cu mm Stained films showed slight anisocytosis poikilocytosis polychromasia hypochromia and some stippled cells The direct Coombs test was negative The white blood cell count was 10 400/cu mm The differential count showed neutrophils 70 per cent lymphocytes 20 per cent eosinophils 6 per cent monocytes 4 per cent There were no lupus erythematosus cells in peripheral blood none after a provocative dose of ACTH and none in bone marrow The liver function tests were normal The total serum protein was 6 7 Gm per cent Serum albumin was 4 2 Gm per cent The serum globulin was 2 5 Gm per cent The urine was normal The electrocardiogram showed sinus rhythm with prolonged P R interval (0 26 second) early left ventricular preponderance and T waves which were rather flat in II lead

Hospital course Eighteen days after admission he complained of severe discomfort over the xiphisternum which he called indigestion Before the nature of this could be discovered he turned pale pulseless and sweaty and collapsed He died shortly afterward

Discussion

PROF ARNOTT Until September 1953 this patient had nothing more than the very common complaint of pain low in the back Then something more definite and crippling appeared He developed pain and stiffness in the joints and began to sweat and feel ill This suggests that he had some sort of polyarthritis I think we must place

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F 1 Mitral and aortic al e aorta and part of wall of left auricle fibrou thickening of both al es and upper part of aortic wall sharply localized bulge a aorta just abov aortic alve (elastic—van Gieson)

particular emphasis on the fact that the proximal interphalangeal joints were in volved in this case for this leads one to believe that he had rheumatoid arthritis He also developed a macular rash well the word macular just means a spot nothing more Strictly speaking it is ap plied to a rash which is not raised above the surface of the body but I think that per haps we must not be too precise about this interpretation Six weeks later his eyes began to feel gritty and became blood shot The fact that atropine and cortisone drops were used suggests that quite a serious view was taken of this disease of the eyes If we take the treatment into consideration together with the descrip tion of the lesion we must conclude that he had something in the nature of irido cyclitis and not a simple conjunctivitis One morning we are told he woke up in the eye hospital with nausea vomiting and vertigo This not uncommon triad of symptoms could mean anything or nothing The therapy with salicylates was stopped which suggests that this treatment was having an excessive effect He then com plained of sensations of an irregular beat ing of the heart The causes of that are usually extrasystoles, paroxysms of tachy cardia or bursts of auricular fibrillation At times he felt as though his heart were stopping these are the sensations of a person who has extrasystoles with a long compensatory pause Somebody took a serious view of this symptom because he was transferred to a general hospital Nevertheless at this time there was no evidence of congestive cardiac failure His systolic blood pressure was a little above normal but his *diastolic* pressure was normal

Eighteen days after admission there was a dramatic development He complained of severe discomfort over the xiphisternum not actual pain and before the nature of this could be discovered he turned pale, pulseless and sweaty and collapsed and died shortly afterward There is one thing *which I think that we can accept at its face value without undue suspicion*—the fact that he was dead! He didn t die *abruptly* he didn t go out like a light as happens when a person develops cardiac arrest or when he breaks suddenly into ventricular fibrillation and the cardiac output falls to zero in a matter of seconds This process of dying occupied some time It suggests to me not a sudden arrest but rather a quite rapid decline in cardiac output Now what does all this mean? One strives always to solve these problems

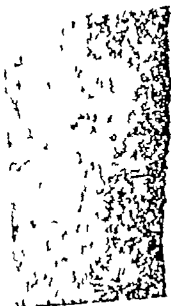


Fig 2 Heavy predominantly lymphocytic and plasma cell infiltration of aortic intima (hematox ylin and eosin, X100)



Fig 3 Aortic adventitia showing similar heavy cellular infiltration (hematoxylin and eosin X100)

on the basis of one logical process This is not always possible because older people often have more than one disease Nevertheless one tries to apply this analytical technique first and this is what I shall attempt to do now

The onset of rheumatoid arthritis is by no means uncommon in his age group and it runs a course just like that described in the clinical summary with swelling of the joints and systemic disturbance to the extent that the patient feels sweaty and ill with fever Skin rashes are not uncommon occurring in about 10 to 15 per cent of the patients The wide variety that may occur include erythema multiforme as in acute rheumatism erythema nodosum or a nondescript macular rash of the type described here Iridocyclitis is also quite common in rheumatoid arthritis and occurs in the same percentage of cases as do the skin lesions One type of iridocyclitis which occurs in rheumatoid arthritis is termed necroscleritis nodosa it presents in a manner very similar to that described in the clinical summary

Now what cardiac disturbances occur in rheumatoid arthritis Pericarditis is occasionally seen and in this case a pericardial friction rub was heard at the apex but when we come to consider and explain the sudden demise of this patient we have to broaden our concept of rheumatoid arthritis This disease is best regarded not so much as a specific entity but rather as coming within a broad group of conditions which merges at one end with the collagen diseases and at the other with polyarteritis nodosa If one extends the concept of rheumatoid arthritis in the latter direction and realizes that polyarteritis frequently coexists with the involvement of the joints we may begin to explain his death He may have had polyarteritis nodosa of the coronary arteries which led to an aneurysm of one of these vessels Such an aneurysm may have bled into the pericardial sac initially this would lead to intense epigastric discomfort such as he suffered There would also have been progressive reduction of stroke volume associated with the filling up of the pericardial sac with blood Finally in the course of this cardiac tamponade cardiac relaxation would have become impossible and the patient would have died in the manner described This is the chain of events that I would imagine might have occurred in this case

Of course he may have had two common



Fig 4 Mitral valve cusp showing marked fibrous thickening and very heavy chronic inflammatory cell infiltration (hematoxylin and eosin X24)

Wassermann reaction was negative In the present case in addition to the changes in the heart and aorta there were changes in the peripheral arteries The left anterior descending coronary artery showed marked intimal thickening adventitial fibrosis and a recent thrombosis (Fig 5) which I assume accounted for his death The right main coronary artery also showed intimal and adventitial fibrosis Of the other arteries examined the internal right and left common carotid arteries were normal The right and left brachial arteries the right and left femoral arteries and the superior mesenteric artery also showed changes Fig 6 shows very marked fibrous intimal thickening in a brachial artery with a very brisk inflammatory response in the adventitia too The areas in the pancreas that I assumed were small fibrosed arteries were in fact ducts that showed a very unusual fibrous thickening (Fig 7) I have not seen such a change previously and it has not been described in any of the published cases of rheumatoid aortitis

PROF ORR I would accept rheumatoid aortitis as a pathologic entity I am rather surprised that Dr Brewer should have described the changes in the aorta as resembling syphilis because on the slide that he showed us the media of the aorta seemed to be singularly free from inflammation

DR BREWER There are at some levels a slight infiltration and vascularization of the outer part of the aorta but I would agree that it is not so extensive as in the case of syphilis It is only about the outer fourth of the media that is involved at any level It is predominantly adventitial

DR HEATH With regard to the mode of death I am sure that many of the audience will be familiar with the histologic changes that were present in the myocardium of this patient They were typical of acute myocytolysis which was described by Dr Howell and discussed at the last clinical pathologic conference of this type in 1960[3]

PROF ARNOTT Yes! I had a sense of *déjà vu* there

DR HEATH Well I think that we may close the conference at that point all agreeing that this is a case of rheumatoid aortitis with involvement of many of the peripheral arteries There seems to have been an unusual agreement between clinicians and pathologists on this occasion!

Diagnosis Rheumatoid aortitis

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Annotations

Atrial myxoma: a diagnostic challenge

During the past 6 years there has been increasingly frequent reports of the successful removal of an atrial myxoma from critically ill patients with pronounced improvement.[1-4] Hence this tumor is no longer to be considered merely as a medical curiosity—a correct diagnosis has practical significance. A myxoma may masquerade as one of several entities: mitral stenosis, bacterial endocarditis, refractory congestive failure, pulmonary embolism, Adams-Stokes syndrome, and epilepsy. Therefore, the chief clinical problem lies in its proper recognition. In review of the case histories of patients with atrial myxomas several diagnostic criteria have been underscored. These are: (1) syncope or severe dyspnea clearly related to change in posture; (2) variations in murmurs from one time of observation to another; (3) change in murmurs related to change in position; (4) unusually rapid deterioration despite careful medical treatment in a patient considered to have mitral stenosis; (5) the detection of myxomatous material in surgically removed emboli;[4] (6) absence of evidence on x-ray examination of chronic passive pulmonary congestion in a patient alleged to have severe mitral stenosis (or when congestion is present, disparity in the degree of venous engorgement in the two lung fields[5]); (7) proportionately little increase in the size of the left atrium as determined by fluoroscopy in the presence of what appears to be tight mitral stenosis. Unfortunately, there have been several cases in which a myxoma was discovered either at autopsy or at atriotomy for mitral valvuloplasty when, despite a careful search, all of the aforementioned features proved to be absent.

Since the majority of myxomas are on the left side, the most frequent error encountered is the incorrect diagnosis of mitral obstruction by such a tumor as mitral stenosis of rheumatic origin. Periodically the medical literature contains accounts of the detection of an unsuspected myxoma during operation for mitral valvuloplasty. Unfortunately, a patient with myxoma of the left atrium may lack all of the features described above and instead show the typical features of valvular disease of rheumatic origin, which include a history of rheumatic fever, loud first sound at the apex, a diastolic rumbling murmur with presystolic accentuation, a typical opening snap, a history of hemoptysis, and evidences of pulmonary hypertension. Conversely, a patient with mitral stenosis of rheumatic origin is often found to have variation in the intensity of the apical diastolic murmur from one examination to another or with change in position. The murmur of mitral stenosis may increase in intensity for several heart cycles after a change to any position, right lateral or upright as well as left lateral, presumably as the result of increased cardiac output during the effort of turning. Finally, a filling defect in the left atrium on angiocardiography may represent atrial thrombus associated with valvular stenosis rather than a tumor mass.

It is apparent that when characteristic features are absent, a myxoma may be indistinguishable from the typical mitral stenosis of rheumatic origin and its discovery delayed until the surgeon inserts his finger into the atrium. Under these circumstances the prudent course for the surgeon would be to resist attempts to remove the mass until he can reopen the atrium under adequate hypothermia[3] or under conditions of cardiopulmonary bypass, preferably the latter. Attempts to remove the tumor mass under the usual surgical setting for mitral valvuloplasty have been unsuccessful with a single exception.

It is hoped that more definitive measures can be developed for the timely detection of intracardiac tumors. Angiocardiography has revealed tumor masses on several occasions and probably represents the most reliable diagnostic technique. However, there have been instances of both false positive[4] and false negative[6] diagnoses with this approach. Furthermore, the use of angiocardiography must relate to some clue sifted from clinical examination, unless one elects the rather unattractive course of performing it on all patients with apparent mitral stenosis.

At the present level of diagnostic acuity perhaps the most worthwhile attitude for the clinician would be to withhold a diagnosis of mitral stenosis until he has made a conscientious search for all of the more unique features which may be produced by a myxoma. This amounts to asking in every case of mitral stenosis: Could this patient possibly have a myxoma? Given any of the features outlined above which are suggestive of an intracardiac tumor, one could justify angiocardiography and propose to the surgeon that an atriotomy be performed under cardiopulmonary bypass.

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The electrocardiogram in ventricular septal defect

During the past few years great deal has been learned about the electrocardiogram in ventricular septal defect (VSD). The electrocardiogram formerly had been thought to be normal or at least of little diagnostic value in VSD. With the introduction of the concept of systolic and diastolic overloading by Cabrera and Monroy in 1952 and the subsequent extension of these concepts by Marsico and co-workers and Sodi Pallares to VSD a new diagnostic era was introduced. Several excellent articles have been published recently which describe the electrocardiographic features in large series of cases of VSD. Of special interest has been the use of the electrocardiogram in evaluating the hemodynamics and in the selection of patients for corrective operation [11]

Four basic electrocardiographic patterns occur in VSD (1) normal (2) left ventricular hypertrophy (LVH) usually of the diastolic overload type (DO) (3) right ventricular hypertrophy (RVH) of the systolic overload (SO) and/or diastolic overload (DO) types and (4) combined ventricular hypertrophy (CVH)

A normal electrocardiogram has been found to occur in 10 to 15 per cent of the cases of VSD [8] Pure or isolated LVH has been found in from 2 to 30 per cent of patients with VSD. Left ventricular hypertrophy of the diastolic overload type (LVDO) is manifested in the left precordial leads (V_5 V_6) by tall R waves with delay in the onset of the intrinsicoid deflection deep Q waves (2 mm or >) and tall T waves [1-4] It has been emphasized (especially in infants and children) that tall R waves accompanied by deep Q waves and tall T waves in Leads II III and aV_F indicate LVH (LVDO) [11] Deep S waves in the right precordial leads (V V_{3R}) are also suggestive of LVH. The deep Q waves have been attributed to septal hypertrophy [4,5] Occasionally the left precordial leads will display inverted T waves (left ventricular systolic overloading) [8]

Right ventricular overloading has been found in from 14 to 65 per cent of the cases of VSD. Right ventricular systolic overloading (RVSO) is manifested by dominant R waves (R R Rs qR) in the right precordial leads (V V) with upright (or inverted) T waves. Right ventricular diastolic overloading (RVDO) is evidenced by the rSR pattern in the right chest leads. Some workers have attributed this rSR configuration to hypertrophy of the crista supraventricularis just as in atrial septal defect

Combined ventricular hypertrophy is encountered in from 20 to 61 per cent of the patients with VSD. It be diagnosed when the electrocardiogram displays the criteria for both RVH and LVH which have just been enumerated. When the right precordial leads display RVH associated LVH may also be suspected if any of the following signs are present in the left chest leads (1) R waves of normal amplitude when lower ones would have been expected (2) prominent Q waves (3) inversion of the T waves in V when T waves are positive in right chest leads

The mean QRS axis in VSD has been found to range widely (occurring in any sextant) although the majority of cases vary from +30 to +150 degrees [5,6] [8] Cases with LVH tend to display normal axis or left axis deviation (LAD) those with RVH tend to have right axis deviation (RAD) whereas those with CVH may exhibit LAD RAD or a normal axis

The terminal QRS forces tend to be rightward in the frontal plane in VSD. This gives rise in the standard leads to the S_1S_2 or $S_1S_2S_3$ pattern in 70 to 90 per cent of the patients

The direction of the frontal plane QRS vector loop tends to follow the direction of the mean QRS axis. Those cases with LAD tend to have counterclockwise rotation of the loop and those with RAD to have clockwise rotation although exceptions occur. DuShane and Kirklin[11] have found that a counterclockwise QRS loop in the frontal plane with a QRS axis ranging from +60 to −60 degrees is usually indicative of left ventricular overloading in infants. Toscano Barboza and DuShane[4] found that 15 per cent of their cases of VSD displayed counterclockwise rotation of the QRS loop above

the isoelectric line (or a figure-of-eight loop, thus horizontal line) similar to that found in patients with atrioventricular cushion defects.[14] This same electrocardiographic pattern has been described recently by Neufeld and associates[15] as being found uniformly in what they term *isolated VSD of the persistent common atrioventricular canal type.*

Katz and Wachtel[16] have described large diphasic QRS complexes in congenital heart disease. This pattern has been encountered (in the limb and/or mid-precordial leads) in from 10 to 72 per cent of the cases of VSD[4,5 ... 12] and has been thought to suggest CVH.[16]

P waves which suggest left atrial enlargement have been found in from 2 to 33 per cent of the cases. Evidence of right atrial enlargement has been found in from 10 to 25 per cent of the cases.

Atrial fibrillation is uncommon in VSD. Complete right bundle branch block occurs in a few cases.[7,8]

Interesting observations have been made concerning the change in the form of the basic electrocardiographic patterns that infants and children with VSD will display when followed for several years. The majority show no change in their patterns. A moderate number of infants with normal patterns or RVH will show increasing evidence of LVDO. This has been interpreted as a normal regression of the increased pulmonary vascular resistance of infancy with the resulting increased pulmonary blood flow and is a favorable sign. Only rarely was pure RVH noted to develop during the period of observation.

The correlation of the hemodynamic and electrocardiographic findings and the role of the electrocardiogram in the selection of cases of VSD for corrective operation has been especially stimulating and rewarding.[19]

Those patients with small defects (small left-to-right shunts, low pulmonary blood flow, and no pulmonary hypertension) have normal electrocardiograms without ventricular hypertrophy.[18]

Those patients who have larger defects (moderate to large left-to-right shunts and increased pulmonary blood flow) have an increased load on the left ventricle, and the electrocardiogram displays LVDO.[20] Such patients usually are good candidates for surgical repair of the VSD.

A large portion of patients with VSD have pulmonary hypertension, either hyperkinetic (due to large pulmonary flow) or due to increased pulmonary vascular resistance (secondary to organic change in the pulmonary vascular bed) or both.[21,22] The pulmonary hypertension will produce RVH, whereas the increased pulmonary blood flow and increased return to the left ventricle will produce LVH so that the electrocardiographic pattern will be one of CVH. However, as long as the electrocardiogram displays good evidence of LVDO there is still usually an increased pulmonary blood flow and the patient will benefit from operation.

When the electrocardiogram shows pure RVH (SO) the pulmonary vascular resistance and pulmonary blood pressure are usually quite high and the pulmonary blood flow is decreased (less than systemic blood flow). Although there are exceptions, surgical repair of the VSD of the patient with this electrocardiographic pattern is usually contraindicated.

Not all workers have found such good correlation between the electrocardiographic patterns and hemodynamic changes in VSD. In fact, even among those who have found good electrocardiographic-hemodynamic correlation there is lack of agreement on the precise electrocardiographic criteria that should be used in the selection of patients for operation.[23]

It should be emphasized that associated anomalies may affect the electrocardiographic pattern in VSD. Although RVH usually indicates pulmonary hypertension, it should also raise the possibility of pulmonic or infundibular stenosis. Electrocardiographic evidence of LVH ordinarily indicates a dominant left-to-right shunt in VSD, but it should be recalled that associated mitral insufficiency, aortic stenosis, or aortic insufficiency may also produce LVH.[24,25]

In summary, it may be stated that the electrocardiogram is an extremely valuable tool in the clinical and preoperative evaluation of patients with VSD. However, it must be emphasized that the electrocardiogram is only one aid and a thorough evaluation of the patient must include a careful history, physical examination, cardiac x-ray examination and fluoroscopy, and in selected patients cardiac catheterization.[19, 20]

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Proposed design for mechanical ECG screening technique

Automatic, mechanical screening or interpretation of electrocardiographic records is a task which has recently captured the interest of various investigators. Although the task proves feasible to some, particularly engineers, physicians who are familiar with the problem tend to regard it as not feasible. At least two research projects are known to be underway (Airborne Instruments Laboratory in cooperation with the Sloan-Kettering Institute, and the Veterans Administration in cooperation with the National Bureau of Standards), both of which are seeking to develop ways of reducing the interpretation of electrocardiograms to digital computer analysis. The National Institutes of Health recently undertook a preliminary study of a similar approach, but has abandoned it (October 1960). A reliable and practical method has not been reported from any source (July 1960 review of the literature). Cardiologists tend to share with physicians in general a distrust of any mechanical or subprofessional procedure which arrives at diagnostic decisions. Their viewpoint is well founded since it is based on a knowledge of the ways in which clinical measurements often show an overlap among normal variations, pathologic states and technical errors. They often insist that the clinical judgment of a physician is needed to make the proper differentiation.

A major impetus which stimulates the search for mechanical methods of interpreting ECG records is the occasional need for screening very large numbers of people. For example, since July 1959 the Federal Aviation Agency has established a requirement that all pilots of commercial airlines undergo serial ECG examinations. All pilots are required to have a baseline record at age 35 and annually after the age of 40. During the first 6 months this rule was in effect a total of 13 000 electrocardiographic records had been recorded, and about 8,000 had been reviewed. The number of ECG records to

be reviewed by the Federal Aviation Agency is expected to reach total of 50 000 annually. The Armed Forces also have a large scale screening problem with both flying personnel and officers in the over-40 age group. The United States Air Force recently reported survey of 67 000 ECG records the Canadian Air Force has reported a survey of a group of 17 000. Various public health projects have also undertaken the large-scale ECG screening of certain populations.

The manpower problems involved in making extensive ECG surveys of large populations becomes nearly prohibitive. Not only is the scarcity and high cost of cardiologists an obstacle but the sheer monotony of large surveys is a deterrent to the recruitment of personnel as well as a threat to the accuracy of interpretation. Mechanical methods for improving the efficiency of utilization of a cardiologist's time appear to be much more feasible at the present time than do methods for achieving a complete mechanical substitute for the cardiologist.

One possible way of achieving a considerable improvement in the utilization of the time of the cardiologist appears to be immediately feasible. A type of ECG pattern exists which for the purpose of the discussion is termed *clearly normal* and which is highly uniform for a large proportion of normal people. In large population of presumably healthy people (such as military personnel and commercial pilots) major portion of the total will be found to be normal of which a large majority will be *clearly normal*. In the large surveys mentioned above for example, it was found that 91 3 per cent of the air line pilots 96 per cent of the United States Air Force pilots and 94 per cent of the Royal Canadian Air Force pilots had normal ECG records. A mechanical means for identifying and sorting out the *clearly normal* records in a large sample would make it possible to eliminate 80 to 90 per cent of the tasks of the cardiologist and thus allow him to confine his attention to the abnormal records and normal variation.

Suggested plan for design of fail-safe device for sorting normal electrocardiograms. A relatively well standardized method developed in one of the nonmedical fields appears to be applicable to this problem. The people in the missile guidance program have developed a method for determining automatically whether radar representation of certain piece of terrain conforms to aerial photos of the area. This map-matching technique can be applied to the matching of ECG records with normal standards. A suggested plan for designing device which will automatically sort out normal ECG records follows.

1 The first step would be to develop a Master Normal ECG Profile thus the limits of which large percentage (the *clearly normal*) of normal ECG records fall. Standards for clearly normal records are sufficiently well defined to render it feasible to establish two-dimensional profile in the form of photographic (positive) transparency. The specifications for this master would be such that substantially large percentage of normal ECG records fall profile-wise within its limits and portions of all other records fall outside its limits.

2 The second step would be to apply the map-matching technique for the purpose of making optical comparisons between the master profile and sample ECG records. Application of this technique to ECG screening would consist of matching the photo-positive master profile with a photo-negative of the sample record. An exact positional match of the two photographs would block the passage of beam of parallel light produced by an optical system. When the master profile completely blocked the passage of light through the sample record a clearly normal ECG record would thereby be identified. Any ECG record of which the profile is different from the master profile or any record with technical imperfection will permit light to pass through the optical system and to activate a photo-electric sensor. The signal resulting from the sensor would then act to separate such a record from those which are clearly normal.

3 The next step would be to prepare the preliminary specifications for an automatic machine to perform the optical matching process. The degree to which it is necessary to normalize the records for amplitude and period would be determined. If it is necessary normalization would be accomplished with the use of a cylindrical lens or by mechanically moving the master profile about either its longitudinal or vertical axis. The fail-safe principle can be incorporated in the process according to which all imperfections all artifacts as well as all records not clearly normal would be sorted out from the clearly normal records. Those not clearly normal would be subjected subsequently to the conventional method of individual examination by a cardiologist.

4 A manual machine could be constructed as a model for the purpose of testing the reliability of the proposed screening method and for making suitable refinements in the design of the system. In particular the model would be useful in making improvements in the master normal profile. When the feasibility of the method has been determined from the manual machine an equipment manufacturer might be included in subsequent plans for the construction of an automatic machine. Finally determinations would be made on the number of lead and the number of cardiac cycles which would be required in order to obtain reliable results.

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Polypeptides, proteins, man, and nature

W thin rec nt year a new field in biochemistry which invol es amino-acid and polypeptide chem istry has unfolded The newly synthesized poly peptides ha e existed in li ing organisms for millions of years but man is just beginning to discover those which occur naturally and to synthesize new ones These amino-acid complexe are potent being active in microgram quant ties Among these are ox tocin asopres in angiotensin II brad kinin and others Many more are to evol e in response t the fancies of those chemist who do research on the proteins and pol peptide and the phy iologic t is destined t enjoy in estigating their man pecific and interesting actions

Not only are ph siologicall potent polypeptide complexes man but so are amino-acid complexes for example t rosine adrenaline noradrenaline isopropyl arterenol noradrenaline 5 h drox trypta mine heparin histamine and other The single modified amino-acid and the multiple amino-acid units re necessary component of the regulators life processes of many organisms including man Most if not all of those listed abo e re extremel potent regulators of cardiovascular function M are y t to be d scovered

The proteins of the bod are much like the w t f the body and nature is the efficient economical nd wise organizer and operator of the lif proc esses Because w ter that wonderf l substance ever present in great bundance in all tes in the body t wise to use it as much as possible for many processes as possible And so t is used It functions are man t transports heat lubricates plits or h drolyzes f t carbohydrates and proteins in most metabolic processes provides h drogen for hydrogen bond and acts as a dielectric It is the great transportation ehicle of cells and metabolic substances (food oxygen and wastes) It cool the body insulates thermally as well as electricall and buffers the body against sudden phy ical and chem ical changes It is plentiful and necessary for lif and is made to serve man necessary life functions

So it ppears for proteins They are ever present in abundance at every te in the body The amino acid are the chemical and physiologic alphabet of living organism the dot and dashes of the physio logic Morse code When the amino acids and their order in the polypeptide chain are varied pecific functional symbols of pecific physiologic responses follow One chain of amino acids (oxytocin) in pecific order (as letters in language or dots and dashes in wireless communication) causes the uteru to contract another (angiotensin II) causes the arterioles to contract and still another (bradykinin) causes the arteriovenous hunts of the digit and skin to con tract and so forth That nature should make so many important uses of a single substance protein and it amino-acid components in a highly temporally organized li ing being such as man should be expected In the development of li ing things from the original fundamental energy of the universe nature should be expected to make as much use as possible of what is lying about to keep the organization imple and t meet readily the needs of the temporally dependent lif processes

It is also interesting to not that in the develop ment of this ystem pecific amino-acid complexes protein are also used as catalyst in the synthesis and digestion of other amino-acid complexes pro teins and polypeptides truly efficient economical and dependable desi n Many important part of cell and organ systems are constructed of proteins which perform interesting fun tions such as con traction of muscle

One ca readil extend these thou hts further not onl for water and proteins but for other sub stances and complexes thereof It exciting to see the new amino-acid alphabet of biochemistry and physiology and t important to note it is this JOURNAL which is devoted t studies of the cardio ascular sy tem

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Book reviews

An Atlas of Acquired Diseases of the Heart and Great Vessels. By Jesse E. Edwards, M.D., Consultant, Section of Pathologic Anatomy, Mayo Clinic, and Professor of Pathology, Mayo Foundation Graduate School, University of Minnesota, Rochester, Minn. With the counsel and collaboration of H. N. Neufeld, R. D. Pruitt, R. I. Parker, and H. B. Burchell. Philadelphia, 1961, W. B. Saunders Company. 1401 pages plus index. Price of 3-volume set, $40.

This work is comprised of 3 volumes as follows: Volume I—Diseases of the Valves and Pericardium (pp. 1-484 plus index); Volume II—Coronary Arterial Disease, Systemic Hypertension, Myocardiopathies, *the Heart in Systemic Disease*, and Cor Pulmonale, Acute and Chronic (pp. 485-984 plus index); Volume III—Diseases *of the Great Vessels (pp. 985-1401 plus index).*

The essence of this work lies in the correlation of functional with structural aspects of acquired cardiovascular disease. Clinical and laboratory manifestations of disease are presented and then related to their pathologic anatomic counterparts.

The material is based on data drawn from case histories of hundreds of patients admitted to the Mayo Clinic over the last 14 years. The presentation is largely pictorial in nature, with discussion frequently in short case-report form. In general the illustrations are excellent. There are over 4,000 reproductions, including pertinent *electrocardiograms, roentgenograms, pressure curves*, diagrams, photographs, and photomicrographs. The text is well written but quite brief.

The cardiologist may find the clinical discussions too superficial, but both he and the cardiovascular surgeon could gain much from the pathologic orientation of these presentations. The price may discourage inclusion of these volumes in personal libraries, but all those involved in the study of diseases of the cardiovascular system should be aware of their availability as reference work. The work is probably best suited for libraries with liberal budgets.

Doctor Edwards is an outstanding and leading authority in the field of cardiovascular pathology. These volumes will contribute to the dissemination of knowledge concerning basic clinical and pathologic interrelationships.

Symposium on Anticoagulant Therapy. Report of the Proceedings of a Symposium held at the Royal Society of Medicine, Nov. 18 and 19, 1960. Edited by Professor Sir G. W. Pickering, M.A., D.Sc., M.D., F.R.C.P. (Lond.), Regius Professor of Medicine, University of Oxford. London, Harvey & Blythe, Ltd. 284 pages. Price 21.

This is a report of the proceedings in book form of a symposium on *anticoagulant therapy held* at the Royal Society of Medicine, England, November, 1960. Each of eight sessions with the panel discussions are published as separate chapters. A total of 54 individuals participated in the symposium; 19 of these presented papers and the others entered into the panel discussions. Although the majority are from Great Britain and the United Kingdom, important contributions were made by Nicola of Italy, Koller of Switzerland, Owren of Norway, and Millikan of the United States.

Only brief discussion is made of the known and theoretical action of anticoagulants on coagulation mechanism and the specific biochemical changes effected by therapy. The discussions, for the most part, are related to the practical experiences in the use of anticoagulants in variety of cardiovascular abnormalities and to the method of controlling the therapy and dosage necessary to provide maximum benefit consistent with safety. Difficulty is experienced in attempting to relate some of these experiences to American medicine because of the differences in methods of practice. Considerable discussion is given to the role of clinical pathologists, the general practitioner, and the consultant in the management of the patients in large clinics, especially in prescribing dosage of drugs.

All admitted that in view of a rapidly increasing number of patients who are receiving therapy, there is great need for a simple, inexpensive, reliable testing procedure sensitive to the multiple factors responsible for thrombogenesis and bleeding. While some gave strong support for and pointed out the advantages of the recently developed Thrombotest of Owren, the majority considered the one-stage prothrombin test of Quick, which is the most widely used procedure, to be the most reliable. Problems with this test, such as its poor sensitivity to some coagulation factors, the variable activity of brain thromboplastin, and the existing confusion in the reporting and interpreting of results, are discussed at length. Advantages and disadvantages of testing capillary blood versus venous blood are discussed.

Impressive statistics for the benefits of long-term therapy in coronary disease are presented by Suzman of Johannesburg and Wood of London; for short-term therapy in the prevention of troublesome venous thrombi and pulmonary embolism in the injured patient by Sevitt of Birmingham; and for long-term therapy of intermittent insufficiency in the carotid and vertebral basilar system by Millikan of the United States. Fewer claims and less enthusiasm are given for therapy in peripheral vascular disease, pulmonary hypertension, and mitral valve disease, and conflicting opinions and experiences are given for therapy of acute cerebral thrombo...

The panel discussions in general are excellent. Differences of opinion and experiences are handled with due consideration and respect but discussed frankly with a good sprinkling of British humor.

This report contains much practical informa-

tion and should be helpful to all physicians who are actively concerned with anticoagulant therapy

MODERN TRENDS IN CARDIOLOGY. Edited by A. Morgan Jones, M.Sc., M.B., F.R.C.P., Director, University Department of Cardiology, Manchester Royal Infirmary; Reader in Cardiology, University of Manchester; Consultant Physician, United Manchester Hospitals. New York, 1961, Paul B. Hoeber, Inc. 264 pages. Price $14.50.

With the welter of recently published books and monographs on cardiovascular physiology and disease, one might wonder how another volume treating of this subject could be produced without trite reiteration. Nevertheless, this volume, skillfully edited by Morgan Jones, presents selected discussions of various facets of cardiovascular physiology in a sufficiently different light to bring them into new focus. The volume is made up of sixteen chapters by British, American, Canadian, and Swedish physicians who are acknowledged experts in their special fields. Each of the chapters has been written in terms of current ideas and the shaping of problems in the selected fields, some of which border upon cardiovascular disease where their importance to circulatory physiology has become apparent. The technical aspects of investigative problems receive lesser emphasis. The net result is a most interesting collection of essays that describe and clarify various physiologic processes of interest.

The book opens with a chapter by Bing on cardiac muscle metabolism. It continues in succeeding chapters with discussions of the circulatory dynamics of the left heart, pulmonary function in heart disease and pulmonary vascular resistance (presented with admirable lucidity), renal function, electrolyte metabolism, metabolic factors in the etiology of coronary disease, congestive heart failure, and certain therapeutic aspects of cardiovascular disease.

This little volume should serve as a reservoir of valuable adjunctive information for students, teachers of medicine, and physicians who wish to broaden their grasp of many of the present trends in cardiovascular investigation and currently important concepts of cardiovascular disease.

Announcement

On January 27, 1962, at the Mayo Memorial Auditorium of the University of Minnesota a scientific program will be presented in honor of the eightieth birthday of Dr. George E. Fahr, Professor Emeritus of Medicine. Papers will be read by his former students, and in the evening at a dinner at the Minneapolis Club his portrait will be presented to the Medical School. Dr. Howard B. Sprague, past President of the American Heart Association, will be the speaker. His topic will be "Dr. George E. Fahr and His Era."

For further information, call or write Arthur C. Kerkhof, M.D., Medical Arts Building, Minneapolis 2, Minnesota.

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